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JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

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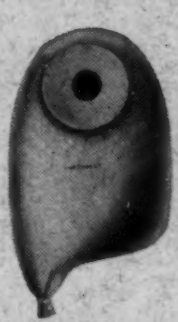

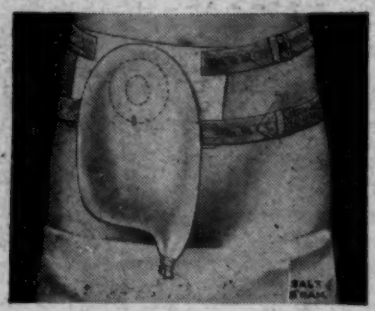

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 6 1954

THE EXPLORATION OF THE CELL IN HEALTH AND DISEASE*

BY

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Quietly but relentlessly a revolution in cellular pathology is taking place. No longer must we be content to regard the cell as a self-contained unit, complex and seemingly imponderable; the first timid attempts at dissecting its structure are now being replaced by bold, nay outrageous, efforts to take the cell to pieces in order to find out what each part does. I will show that the cell membrane, the nucleus, and even the smallest formed elements—the mitochondria and microsomes—no less than the by-products of cell activity, can be separated from their usual habitat without any too violent disturbance and studied as entities. And there are signs that an even more remarkable procedure is on the way to exploitation. Not only can the all-important nucleus of a cell be removed but another nucleus from a closely related cell can be put in its place, thereby enabling that cell to carry on its function for at least some time.

A new Form of Pathology

Side by side with these micro-anatomical developments have come astonishing inventions in the field of biochemistry and biophysics which are invigorating the momentous domain of function. We now may contemplate a new form of pathology based on an intracellular physiology which in turn is built up at a submicroscopic, indeed a molecular, level. Let me show what this revolution means by a reminder of the landmarks in the history of the cell.

The first vague impressions that life might derive from simpler, unitary forms took on substance when the imperfections of the early microscopes were corrected around about 1830. Cells were then quite clearly seen, and within 20 years assumed new rank as living, dynamic units. At this time, too, arose cellular pathology, which was welded with astonishing prescience into a vigorous science. A century of progress followed which was devoted largely to the microscopical scrutiny of the cell, especially its interior and its derivatives. The harvest was a remarkable one, for the morphological elements were discovered, something was learnt about their functions, and the first steps towards an understanding of organization and chemical constitution of the parts were taken. Methods, however, were relatively crude and for the most part indirect.

This century has seen the invention of new tools which are still in process of exploitation. Isolated single and small groups of cells are now accessible to respiratory and metabolic investigation as the result of the ingenious experiments of Linderstrom-Lang, Holter, Zeuthen, and O'Connor. Microsurgery and differential centrifugation enable us to separate the various morphological constituents from the parent cell and with the aid of chemical refinements subject them to analysis. Cytochemistry and enzymology are being pursued vigorously with the object of learning more about intracellular respiration and metabolism. With the perfection of the electron microscope we may now learn about the molecular dimensions of the cell and its organelles; in this task we are assisted in a less specific fashion by the discoveries of polarization optics and *x*-ray diffraction. To the pharmacologist and immunologist we owe a great debt for the laying bare of unsuspected regions of the cell that are vulnerable to drugs, hormones, and antigens, while few can consider unmoved the ingenious researches of the neurophysiologist whose analyses of electrical responses penetrate to the very heart of specialized cellular function.

Now, I am sure that pathologists will not allow this surge of discovery to pass unnoticed over their own particular province; indeed, I see many signs that the impact is already producing steady results. But I fear that progress is slow and the young worker may be overwhelmed by the heavy burden of facts with which he is faced when he decides to take up pathology as his life's work. For these reasons I am encouraged to say something of what I am learning through contact with the fresh young minds of my assistants and other friends who are taking an active part in this field of endeavour. We shall embark upon a voyage of exploration of an ocean which is to a large extent uncharted. I trust that the end of our voyage will see us a little clearer about the direction in which we are going and encourage us to venture still further into the unknown. Clearly, in making this journey we must have a compass by which to steer, something that will give us a steady sense of balance and direction. Let this be our endeavour to discover "identity amidst diversity," or the Kantian doctrine "to understand nature by means of exact concepts." Plato said that if he met the man who could detect the one in the many, he would follow him as a god. May that be our precept in the short time we spend together.

The Cell Membrane

Much that we know about the cell membrane comes from studies on the passage of diffusible solutes such as common salts and solvents, especially water, into cells and, above all, on the exchange of molecules and ions between cells and their environment. It is precisely at the cellular

*The first Matthew J. Stewart Lecture, delivered at Leeds, June 17, 1954.

surface that the first obstacle to penetration of the cell is encountered, and we are led to ask why this should be.

Direct examination of the cell membrane has, up to the present, proved possible only in the mammalian red corpuscle, from which most of the cytoplasm can be removed as the result of haemolysis, leaving behind what appears to be a true membrane almost free from intracellular material. Under microscopical examination with dark-ground illumination or with polarized light this thin structure stands out brilliantly, displaying no signs of internal structure. Chemical analysis of these ghosts tells us that much lipid and protein is present; the ratio of total lipid to protein by weight in the ghosts of beef red cells turns out to be 1 to 1.76. All types of lipid are found, though phospholipids form the highest proportion and constitute, with cholesterol, over 90% of the total lipid. Apparently the phospholipids are strongly bound to the protein, but portions of the cephalins, for instance, are loosely bound and can be readily extracted.

By making certain assumptions about the molecular weight of the protein—for example, that its molecular weight is not less than 70,000—we can calculate that there are some 70 lipid molecules for every protein molecule present in the membrane, and, of these, 32 molecules are cholesterol and 38 phospholipid. The latter are further divided into 27 cephalin, 7 lecithin, and 4 sphingomyelin molecules per protein molecule. The plasma membrane of red cells thus has a relatively large number of lipid molecules loosely or firmly bound to each protein molecule.

Calculation also gives some idea of the thickness of the plasma membrane concerned in permeability phenomena, and it seems to be between 50 and 60 Å. This may well be made up of a double layer of lipids accounting for 30 Å of thickness and a protein layer which when dried measures 20–30 Å. To these must be added an unknown quantity of water.

Through such a membrane water diffuses with great rapidity along aqueous channels in the membrane. There are indications, too, of other kinds of space, for if the haemolysis of red cells during unfavourable osmotic conditions is followed by means of high-speed photography, it is found that haemoglobin molecules escape uniformly all over the cell surface not unlike water through a sprinkler. Under other conditions, however, the surface of the cell can be made to burst with extrusion of haemoglobin at one point. Uniform loss from many points requires that the channels through which haemoglobin diffuses to the exterior be uniformly spread over the surface of the cell.

These facts may be reconciled in a three-dimensional model, composed of an interlacing meshwork of protein molecules, possibly two molecules thick, with interspersed lipid molecules bound to the protein or to each other and forming a porous entity. These pores vary in diameter, show a water channel near to the protein and phospholipid molecules which leads from the external environment to the cell interior, and probably number 3,000 to 300,000 in each cell membrane. Quite likely, too, there are water pools in addition to these channels, which account for the speed with which haemoglobin molecules leave the red cell during haemolysis. Lipid molecules bound to protein have been pictured as swinging out of position during haemolysis so that the pools become continuous with the water of the external environment and of the cell interior (Parpart and Ballentine, 1952). The strongly bound lipid molecules in the plasma membranes may thus behave in the manner of a swinging door, hinged by their head attachment to the protein and caught at their outer edge by interaction with long-chain fatty acids of weakly bound lipid. In this way pores can vary from time to time in their dimensions in the same cell. So, too, they may vary in size, number, and water content from species to species, thus accounting for the manifold permeability differences that have been noted by many workers.

A wealth of observation, accumulated since the pioneering studies of Pfeffer and Overton, has taught us some of the principles that underlie this business of penetration of cells by solutes. Overton deserves the credit for recognizing that an organic molecule can be so changed that its affinity for certain organic solvents as compared with water tends likewise to increase with its ability to enter living cells, even though there is at the same time an increase in its molecular weight and volume (Jacobs, 1952). If, for instance, chemical groups such as CH_3, C_2H_5, or C_6H_5 be attached to the molecule, then that molecule will, in general, penetrate the cell more rapidly although it is enlarging. The cell surface invariably contains large amounts of lipid which serves as a solvent for many hydrocarbons. In other words, possession of lipid-soluble characteristics promotes the power of penetration through the cell membrane by the compound under consideration. So, too, a non-aqueous barrier presented to the external environment by the bound-lipid molecules would normally confine the passage of lipid-insoluble molecules to the aqueous channels.

The size of a soluble molecule may also exert an important influence on its capacity to enter cells. A porous membrane would thus behave as a sieve, allowing some molecules to pass through and holding others back. The water pools together with the aqueous channels thus may well determine the rate of penetration of lipid-insoluble molecules and the limits of molecular size for penetration.

Another possibility exists in the form of specific affinities possessed by certain compounds for the surface of some particular cell or cells independent of lipid solubility and molecular size. Urea, for instance, has a very high permeability value for mammalian red blood corpuscles which has nothing to do with lipid solubility or molecular value. So far little has been learnt about these affinities. In some cases special enzyme mechanisms may be concerned as with the entry of glycerol into bird red corpuscles (Jacobs, 1952). Thiamine, too, is first adsorbed to the surface of yeast cells to be incorporated into the cytoplasm only after phosphorylation (Sperber, 1941). Selective ion passage across the cell membrane most probably is a matter of selective charge on the aqueous channels (Michaelis, 1925).

But even the penetration of water into many cells is not the straightforward matter of osmosis, since it now turns out that it is exceptional for cells and their contents to be in osmotic equilibrium—that is, isotonic—with their extracellular environment (Opie, 1949). Largely owing to the recent researches of Krebs and his colleagues and Robinson (1950, 1952) we suspect that cell respiration governs the water balance because some of the energy which it releases is used for active transport of water out of the cells through the mediation of compounds containing high-energy phosphate bonds. Robinson points out that if the contents of cells are hypertonic then there must be an active transport of water outwards across the cell membrane, for inward transport of solutes through a membrane freely permeable to water could hardly account for a sustained difference in osmotic pressure and would cause the cell to swell continuously. Active transport probably also applies to loss of potassium and other ions. Thus there would appear to be pumping mechanisms bound up with cell respiration situated quite likely in the cell membrane, but we have no knowledge of their precise location.

These modern views are of great interest for the pathologist, especially since Robinson has given us a new lead regarding the explanation of intracellular accumulation of fluids. Pathological experience shows that a poor oxygen supply to cells of most organs is followed by cloudy swelling and hydropic change, the main feature of which is water-logging of the cells. Robinson suggests that cloudy swelling might arise primarily from derangement of the active transport of water which normally maintains the volume and the hypertonicity of respiring cells. This ingenious theory would certainly account for the frequent association of cloudy swelling with anoxia.

The cell surface is probably a mosaic of patches composed of proteins, lipids, polysaccharides, extremely variable from species to species, but possessing, we have seen,

features common to all cells which control the interchanges between cell and environment. Unique among these components are the surface enzymes. Part, at least, of cell respiration, in the broad sense of oxidative breakdown, takes place at the cell surface; later on we shall see that part, too, is concentrated within the cell in the mitochondria. The cell surface has been likened by Runnström to a cell organ, but unfortunately we know nothing about its intimate topography. There is every reason to believe, too, that the cell surface is capable not only of secreting and expelling components, but also of releasing substances to the endoplasm which may influence the behaviour of distant regions within the cell. But we come up against an almost unexplored territory here, and we must await new discoveries before embarking upon new theories.

Pharmacological Discoveries

Before passing on to fresh regions of the cell, allow me to recall a few of the discoveries made by pharmacologists which have their lesson for the pathologist. I would remind you of the growing opinion that effective drugs react first with specific surface constituents, patches, or receptors, and that this association leads secondarily to changes in the pattern and function of other parts of the cell (Loewi, 1952). An elegant proof of such surface action is to be seen in some experiments carried out by Cook in 1926 and based on the use of methylene blue. This dye can penetrate heart cells to produce deep staining of the cytoplasm and also exerts an atropine-like action on the heart cell. If the heart be deeply stained with methylene blue and then washed thoroughly to remove any dye outside of the muscle cells the atropine-like action ceases, although the heart remains deeply stained. But the action returns precisely at the very moment a trace of methylene blue is added again to the preparation, which means that the cell surface is the region responsible for the atropine effect.

Further evidence in favour of specific surface patches comes from the calculation of the extremely minute quantities of drugs such as acetylcholine and adrenaline capable of exerting cell stimulation. Some years ago Professor A. J. Clark calculated that acetylcholine in effective amounts covers only one six-thousandth part of the cell surface, a conclusion difficult to assess except on the assumption of sensitive patches. No doubt such enzymes as cholinesterase are located at the cell surface in such patches.

Proteins, too, are supposed to act at the cell surface, though some reach the interior by phagocytosis or after injuring the point of contact. The latter seems to be the case with some viruses and toxins. Proteins marked with isotopes—for example, I^{131}—can penetrate renal tubule cells during excretion, as my assistant, Dr. W. G. Spector (1953) has shown, but it is not known whether such cells are normal or damaged. Most proteins, we would expect, would not be able to diffuse into intact cells because of their large molecular weight. Some sort of combination with surface constituents may initiate the cell response in these instances, as, for example, in the Dale experiment with the sensitized uterus reacting instantaneously to the specific antigen.

Let me here recall certain observations that may bear upon the action of poisons on cells. With refinements of quantitative methods we have learnt that cell permeability may be profoundly modified by changes in hydrogen-ion concentration and temperature variations. Extremely low concentrations of copper instantaneously lower the permeability of human red blood corpuscles for glycerol (Jacobs, 1950) due to inhibition of an SH-containing enzyme apparently concerned at the cell surface in a metabolic process which yields the energy for the uptake of part of the glycerol (Le Fevre, 1948). Again, it is surely suggestive that heavy metals such as arsenic and mercury inactivate the SH group of enzymes containing that group as an essential part. Other drugs interfere with enzyme activity by competing either with substances physiologically acted upon by enzymes—substrate competition—or with elements needed for the synthesis of enzymes. Hydrogen cyanide, for instance, combines reversibly with the iron of the haem forming the prosthetic group of oxidizing enzymes and thus prevents those enzymes from being renewed. Tannic acid is an example of a poison that acts on the protein of the surface pores, decreasing the amount of water within the water channels, and profoundly modifying cell permeability (Jacobs).

Finally there is an interesting group of bacterial toxins whose precise action on the cell membrane is being elucidated by workers in this country. Foremost among these is Professor C. L. Oakley, whose researches have done so much to show that lecithinases are largely concerned in the action of certain clostridial toxins. *Cl. welchii* α toxin is now known to be almost certainly a specific lecithinase that can exert lethal, haemolytic, and necrotic effects in susceptible animals. The haemolysis of horse and sheep red corpuscles by this enzyme has been shown by Dr. Marjorie Macfarlane (1950), of the Lister Institute, to be always preceded by decomposition of some of the phospholipid of the cell, much of which, we have seen, resides in the cell membrane. The enzyme fits into the cell surface in which the substrate, phospholipid, is embedded. The lecithinases vary in their activity with different species of red cell (Oakley *et al.*, 1947), and this may well be due, as Dr. Macfarlane suggests, to differences in configuration amongst the lecithinases on the one hand and amongst the species-specific red corpuscles on the other. Such investigations are likely to throw light not only on immunological differences between bacterial species, but on the structure of the cell membrane.

The Cell Nucleus

It would scarcely seem possible that doubts should exist in our minds about the main functions of the nucleus. For more than 150 years contributions to nuclear knowledge have been unending, and we take it for granted that, as Mazia (1952) has so well put it, "the cell without a nucleus is a cell without a future." Yet what do we really know about the nature of that unique intracellular organ, save that within its confines go on great perturbations of cell energy from which come rifts in intranuclear and cellular structure which ensure the propagation of the species? Let me consider for a few moments the sum and substance of our knowledge about this mysterious body in the light of recent investigations.

Methods now exist whereby the nuclei of many cells may be isolated from their correlated cell structures and studied as isolated entities. Electron photomicrographs of isolated nuclear membranes have been obtained and present evidence that such membranes consist of two layers, an inner homogeneous film and an outer porous layer with pores of 400 Å diameter regularly arranged at 1,000 Å intervals (Callan *et al.*, 1949; Callan and Tomlin, 1950). Some at least of these membranes seem to be freely permeable to molecules of subcolloidal dimensions (Goldstein and Harding, 1950), so that it is possible that a wide variety of toxic compounds may be able to pass into the nuclear substance as well as being able to exert an influence on the membrane itself. In this way chromosomes, which are elastic structures enclosed in a limiting membrane, may become the targets of radiations and nuclear poisons, but no one can say at present what is the mode of action of such agents on the chromosome. Until we know more about chromosomal membranes and internal structure we can scarcely hope to follow the biochemical intricacies of chromosomal injury. Electron-microscope investigations show no structure that was not previously known, nor is there any evidence of orientation of smaller units forthcoming from *x*-ray diffraction studies.

Nuclear enzymes have been the subject of intensive investigation recently. Here, too, isolated nuclei have been employed, and with startling results, for it seems that no case has been encountered in which an enzyme is exclusively localized in the nucleus, or in which even the greater part of the cell's supply is concentrated in the nucleus. Even more unexpected is the discovery that enzymes peculiar to

energy-yielding processes are either absent or remarkably low in concentration. This applies in particular to the glycolytic system, succinic dehydrogenase, and cytochrome oxidase. On the other hand, there are a few systems—for example, alkaline phosphatase, desoxyribonuclease—which may be present in higher concentrations in the nucleus than in the cytoplasm. Probably the nucleus is concerned with the long-term continuous replacement of the cell activities, for turnover of metabolic intermediates and proteins has been demonstrated but not of cytoplasmic enzymes or enzyme groups (Mazia). Such replacements would require the transfer of some nuclear product to the cytoplasm; there is reason to believe that this is true of material rich in ribose-nucleic acid from certain chromosomes to the periphery of the nucleus and thence to the cytoplasm (Caspersson, 1947; Brachet, 1950). So far as its energy supply is concerned, the nucleus might be said to be parasitic on the cytoplasm (Mazia).

It is now possible to remove the nucleus successfully from the living cell or unicellular organism—for example, amoeba—and even to transplant a nucleus from an intact cell into one deprived of its nucleus (Comandon and de Fonbrune, 1939; Mazia, 1952; Lorch *et al.*, 1952; Lorch and Danielli, 1953). After enucleation, various cell activities go on uninterruptedly, while others continue for a time. Amongst the former are amoeboid movement—although movement may be uncoordinated—cytoplasmic streaming, co-ordinated ciliary movement, photosynthesis. Synthetic activities and secretory functions involved in the capture and digestion of food continue, but soon become ineffective. With some forms of life, the enucleated portion of the cell makes a start towards regeneration, but apparently it cannot carry this to completion (Haemmerling, 1934). The enucleated *Arbacia* egg is not abnormally permeable to water nor is enucleated *Amoeba proteus* or pieces of enucleated amoeba abnormally permeable to D_2O (Prescott and Mazia, 1954).

A cell that has been without its nucleus for three days recovers in all respects when it receives another nucleus, and can produce many offspring. This shows that the cell can persist unchanged in its normal function throughout a short period when deprived of its nucleus. After an interval it begins to run down and it eventually dies because synthesis and absorption give out.

I confess I am puzzled by the application of these discoveries to cellular pathology. I think that most of us have been brought up in the belief that nuclear damage, as displayed by the familiar disturbances of karyorrhexis, pyknosis, and karyolysis, is an early and serious sign of cell injury, from which there is seldom recovery. Now it seems that cells may survive for many days without a nucleus, presenting no obvious morphological disturbance and very little functional decline. Surely the time has come when we must reconsider the nuclear field and be prepared to discard much of what we have long held to be established.

Mitochondria

Among the most interesting discoveries in cytology that promise revolutionary advances are those which concern the mitochondria. Despite a long period of uncertainty about their very nature as entities, and the clash of rival views touching their functions, we now possess clear evidence that they are important cell organelles which can be isolated and studied apart from other cell constituents and used as tools for the investigation of toxic agents. It is the latter enterprise that I wish to embark upon, for I believe that here lies to hand a vast unexplored region of cellular pathology. But before doing so, let me mention what we have learned in recent years about the properties of normal mitochondria.

When living cells are subjected to centrifugal forces several hundred thousand times gravity they display a high resistance to disintegration, which suggests that cytoplasm or, at any rate, the cortical zone of cytoplasm consists of a framework capable of deformation but not disruption by the strong centrifugal forces (Beams, 1943). Nevertheless, a certain amount of stratification of cell contents occurs under these conditions, and organelles and other cell contents become arrranged in various layers, as might be expected if the milieu possessed a gel structure (Runnström, 1952). Since these displaced organelles return to their usual locations after centrifugation is over, it seems more than likely that a great deal of give and take must exist within the cyto-skeleton, a view that is supported by the cell's possession of movement, the complex phenomena of mitotic division, and the expansion and collapse of vacuoles. All these observations prepare us for the discovery that mitochondria are, indeed, entities in which are localized special functions.

The early studies on tissue culture cells, especially the use of cinephotography for the recording of structural change in living cells, taught us that mitochondria vary from granular to rod forms from moment to moment, seeming to anastomose and assuming bizarre patterns and even dividing when the cell divides (Lewis and Lewis, 1915; the Canti film; Hughes and Fell, 1949). These apparently pointless facts received fresh significance when, with the invention of new methods for the segregation of organelles, mitochondria were isolated and their functional capacities laid bare to investigation.

Two such methods are in common use. Holter and his co-workers centrifuge cells or unicellular organisms at 1,000–2,000 *g* for 30–60 minutes and separate cell fragments containing concentrates of various cytoplasmic constituents by means of micro-needles (Holter, 1954). The method has the advantage of being less apt to produce artifacts than more violent centrifugation, but the amount of material so obtained is very small and such cytoplasmic samples are never pure. Although still in the early stages of improvement, this technique has already yielded valuable results which are complementary to those obtained from other studies.

The second method is much more ruthless, for the tissue is homogenized after freeze-drying, and then subjected to differential centrifugation whereby the particulates of the disrupted cells are isolated in practically pure form. Since there is a tendency for the granules to agglutinate during centrifugation isotonic sucrose is used for suspensions, and this proves satisfactory without disturbing the osmotic relationships between particulates and medium. Mitochondria are spun down by centrifugation for 20 minutes at 24,000 *g*; finer particles still, the so-called microsomes, are obtained from the supernatant after centrifugation for two hours at 41,000 *g*. These methods, developed largely by American and Belgian workers, allow of the quantitative fractionation of the whole cellular body; indeed, an essential safeguard of the method requires that the sum of each distinct component thus separated must account at the end, in mass or specific activity, for the total cell mass or the total specific activities exhibited originally by the unfractionated cell (Claude, 1954). In other words, a balance sheet must be struck which shows how much of a function is accounted for by each fraction in terms of the total activity of the cell under consideration.

In my department, we stick closely to the methods laid down by Claude, Lehninger, Hogeboom, and their collaborators, employing a machine capable of differential centrifugation up to 60,000 *g*. Photographs of isolated mitochondria in isotonic sucrose show them to be yeast-like bodies with little structure, but the recent electron-microscope studies of Pallade and Beams indicate a limiting membrane and a complex pattern of leaves and compartments not unlike that of a beehive. Mitochondria are profoundly influenced by changes in the salt concentration of the medium in which they are suspended, for they swell enormously and break up in hypotonic saline or distilled water in much the same way as do red corpuscles (Claude). Recent studies by Dr. W. G. Spector on electrolyte flux in mitochondria during the action of lytic and spherulating agents confirm the view that isolated mitochondria behave as osmometers.

Chemical Composition

Chemical analyses of lysed mitochondria show them to be complex in their composition: 25% of their substance is lipid, especially phospholipid; a protein fraction which includes their important "soluble" enzymes and a dialysable fraction represented by ribose nucleic acid have been separated. It seems that one-third of the total nitrogen and one-fifth of the ribose nucleic acid of rat-liver cells repose in their mitochondria. And there is reason to believe that mitochondria in turn may be broken down to smaller particulates, about 0.1 μ in diameter, which carry nearly all of the complement of ribose nucleic acid possessed by the parent elements. We are thus confronted with cell elements in the form of mitochondria which are built up according to a specialized pattern in which are concentrated lipids, rich in phosphorus, and ribose nucleic acids.

But it is the enzyme systems which point the way to the elucidation of mitochondrial function. You will recall a most unusual discovery that was made by Warburg over 40 years ago when he demonstrated that cellular oxidations may be bound to granules. It now seems certain that such respiring granules are, in very truth, mitochondria, for localized within isolated mitochondria have been discovered enzyme systems which enable molecular oxygen to be utilized. Cytochrome oxidase exists exclusively there; indeed, about 80% of the total cellular cytochrome oxidase activity can be traced to the mitochrondrial fraction. Claude (1954) attributes 70% of succinic dehydrogenase activity and 50% cytochrome c to the mitochondria, and thinks that oxidative phosphorylation processes are restricted to them. The enzymes of the Krebs tricarboxylic acid cycle are also present. It has been shown that energy released in these oxidations is transferred to energy-rich phosphate bonds and these can be built up within the mitochondria and sent out to other regions of the cell. Co-enzymes such as di- and tri-phosphopyridine nucleotide and flavine-adenine nucleotide are important components present in bound form; they supplement the activity of the oxidative and phosphorylating processes. Small wonder is it, therefore, that Claude labels mitochondria as the main power plants of the cell, because they utilize molecular oxygen and distribute energy-yielding components to other organelles.

The studies of Krebs and his colleagues with radioactive tracers indicate, too, that a continual exchange goes on between the ions of the mitochondria and the suspending media. Thus the whole of the mitochondrial Na and K can readily be replaced by that of the environment. In some of these exchanges the expenditure of energy is concerned notably in the uptake of inorganic phosphate, as is the case, it will be remembered, with heart muscle or red cells; in other instances the exchange recalls that which occurs across a semi-permeable membrane in a Donnan system. Krebs suggests that mitochondria may be the basic units responsible for secretory and absorptive activity of cells. Secretion, therefore, is a process that takes place not only in glands but perhaps in all cells. Absorption, too, may well be a common feature of all cells. At the heart of these processes stand the mitochondria, which are thus not only the sites where most of the available energy is generated, but the mechanism whereby this energy is directed into channels for the transport of solutes and the maintenance of secretory and absorptive activities (Bartley *et al.*, 1954).

Researches into Mitochondrial Function

I have spent some time in viewing the advancing tide of investigation into mitochondrial function because I believe that it is in precisely this field that fresh discoveries may be anticipated that will be of vital importance for cellular pathology. In support of this claim I will describe briefly some of the indications that influence my belief.

For some time now my assistants have been interested in the effects produced by poisons on the liver. Recently Dr. J. D. Judah and Dr. G. Christie, of Melbourne, have completed an important study of the action of carbon tetrachloride on liver cells which, to my mind, throws a great deal of light on these matters. Briefly the outcome of their investigation is the theory that this fat-soluble agent enters liver cells, attacks the mitochondria physically so that they lose their power of retaining their small stores of enzyme co-factors (pyridine nucleotides especially), and this results in the disorganization of the chain of enzymes constituting the tricarboxylic acid or Krebs cycle. In consequence, a loss of the integrated enzymatic activity necessary for the production of energy in the cell follows, as one would expect from our knowledge of mitochondrial function, despite the fact that individual enzymes may still retain activity. Most of this work has been done on isolated mitochondria, but Christie and Judah (1954) have shown that quite likely similar damage is induced within liver cells when a rat is exposed to a toxic dose of carbon tetrachloride. It will be remembered that within a few hours of such an exposure liver cells swell and develop clear vacuoles which may extend throughout the greater portion of the cytoplasm. These are filled with water and a little emulsified fat, and some pathologists have long believed that they arise from mitochondria.

My assistants have actually separated the vacuoles from their parent cells by centrifugation and proved that they possess the characteristics of altered mitochondria. Christie and Judah found that mitochondrial respiration is diminished by carbon tetrachloride poisoning as the result of bottlenecks at certain phases of the tricarboxylic acid cycle as well as at some stages of breakdown of fats. Since these mechanisms lie at the very foundations of water, fat, protein, and carbohydrate metabolism, is it any wonder that cell function is grossly disturbed and that water and fat, and quite possibly products of protein breakdown, accumulate within the cell to give the well-known morphological changes associated with carbon tetrachloride damage? My assistants have also shown that choline delays the onset of the enzymatic changes, and this may be the basis of the prevention of fatty liver associated with chronic carbon tetrachloride poisoning.

Isolated mitochondria have also been used by Dr. W. G. Spector in investigations of the action of lytic and spherulating agents, and he has shown that under such conditions mitochondria lose much of their potassium and some of their sodium while retaining magnesium and calcium. Potassium loss is prevented by suspending isolated mitochondria at 37° C. in a medium which allows oxidation of tricarboxylic acids and the coupled phosphorylations to go on. This suggests that the retention of potassium by normal mitochondria against a gradient depends upon the associated metabolic activities, and Spector has demonstrated that it is oxidative phosphorylation which maintains the potassium concentration against an adverse gradient. This recalls similar phenomena in red corpuscles where potassium loss accompanies ageing or damage, but in that case, as Maizels (1949) has taught us, a glycolytic mechanism is concerned in preserving the potassium concentration. All such studies convince me of the importance of these organelles for the economy of the cell and indicate their sensitivity to injury of various kinds. We still have a long way to go before we can express cell response to abnormal conditions in terms of precise biochemical reactions, but I think you will agree that an encouraging start has been made. At the moment, Dr. Judah and Mr. Gallagher, of Sydney, are endeavouring to find out more about cell behaviour in the presence of certain dietary deficiencies, especially copper, and their results already promise a valuable harvest. We have planned other investigations in this field which range over many fascinating facets of pathology, but it would be premature to mention them.

"Lethal Synthesis"

I am tempted to include here a short reference to the brilliant studies of R. A. Peters and his school at Oxford which have led to the introduction into the theory of disease of the new concept of "lethal synthesis." As the outcome of his investigations of fluoroacetic acid (FCH_2COOH), a

compound which is the toxic principle of the South African poison plant known as gifblaar (*Dichapetalum cymosum*), Peters has shown that this substance induces a purely biochemical lesion in the cell. It does this through an enzymic block in the tricarboxylic cycle, the enzyme involved being aconitase. In this way the metabolism of both carbohydrate and fat within the cell is "jammed" at the tricarboxylic acid stage with the consequent increase of citrate inside the cell and the slowing or stoppage of metabolism. The astonishing thing is that fluoroacetate itself is not toxic to enzymes. The trouble arises through fluoroacetate being misguidedly synthesized by enzymic action, into a fluorotricarboxylic acid, probably fluorocitric acid, and this inhibits aconitase in minute amounts. Thus a compound apparently harmless in itself is joined with relatively innocuous cellular metabolites to bring about serious disturbances of cell function. Peters suggests that the latter takes place in two ways: (1) by the reduction of the energy supply by "jamming" of the tricarboxylic cycle, and (2) through the immobilization of Ca ions by the increasing citrate concentrations in the cell with altered cellular excitability, especially in the case of nerve cells.

Such a "lethal synthesis" contrasts strongly with the classical protective syntheses in which molecules foreign to the organism are converted to less toxic compounds. With fluoroacetate we are confronted with a substance that "can so deceive the normal metabolic enzymes concerned with getting energy into making a substance which will poison them, and only then because the enzymes are organized in the mitochondria" (Peters, 1952). I feel sure it will be agreed that Peters has given us a new lead in cell pathology from which may come many fascinating discoveries.

I now turn to the last of the cell components that I have chosen for consideration, the tiniest and least investigated of the organelles, the microsomes.

Microsomes

Cytologists have long been aware of the existence of minute cell components that lie just on the fringe of microscopic dimensions. In some cells these take the form of tiny granules which contribute to the underlying staining reactions of the cytoplasm, even imparting a distinct basophilic element to the more usual acidophilia. With the coming of differential centrifugation, elements of the cytoplasm that are submicroscopic in their dimensions have been separated from every active cell, and these, without doubt, correspond to the minute cell structures that were long sensed to exist. They have been named microsomes.

Microsomes range in size from 60 to 250 mμ and make up as much as 20% of the dry cell mass. They consist of delicate vesicles or slender strands which fragment easily, and in so doing they release part of their soluble constituents. They, too, are rich in lipids—as much as 40% of their mass is lipid, over two-thirds of which is phospholipid—and they contain 50 to 55% proteins (Claude). At least 50% of the total ribose nucleic acid of the cell is associated with the microsomes, and this no doubt is the reason for the basophilic tint of the cell ground substance. Microsomes must therefore be important centres for protein synthesis in the growing cell, especially for ribose nucleic acid production, and labelled amino-acids have been shown to be incorporated within them, probably taking part in forming peptide bonds within the protein molecules (Greenberg *et al.*, 1948). However, they are poorly off for enzymes except in the kidney, where certain phosphatases —glucose 6-phosphatase and alkaline phosphatase—appear to be closely associated with microsome fractions. Their osmotic behaviour suggests that they are enclosed by a semipermeable membrane. Since this is the extent of our knowledge at the moment, we can do no more than conjecture their function. My object in drawing attention to them is to urge the need for further investigation of what may prove a rich field of pathological discovery. I know of no information about microsomal reactions to injurious agents; I can only ask whether they, too, play a part in the cellular degenerations, if they are linked closely to the mitochondria or the nucleus in co-operative function, and speculate that they may be concerned in the storage and production of hormones, antibodies, and other secretions.

Conclusion

My survey of these selected topics of cell behaviour has reached its end, and I am faced more than ever with feelings of insecurity and incompleteness. But can the position be otherwise when a field of investigation is making such rapid strides forward? Rather may we not find grounds for congratulation in the uncertainties and dissatisfactions of modern cell theory and of cell pathology in particular, provided we never cease to give up the attempt to eliminate or to rectify our illusions?

But this is not the way to end a lecture such as this, and I must return to my initial plan and attempt to convince you that some progress has actually been achieved. I set out with the purpose of trying to decide whether we really understand how a cell is injured by a poison, whether it be chemical, in the ordinary sense of the word, or toxic, the product of living matter. Let me say at once that I am sure of some success. In support of this optimism, allow me to draw a simplified sketch of how a poison such as carbon tetrachloride—or its close relative chloroform—brings about its harmful effects on one type of cell.

When carbon tetrachloride is brought to the liver in the blood plasma, partly in solution, partly attached in unexplained fashion to the blood lipids, its capacity to penetrate the cell is determined by its lipid and water solubility, its molecular size, and possibly other factors about which we know very little. It will thus be thrust along the pores of the surface sieve by way of the water spaces and in intimate contact with the lipid lining of the pores. Some molecules will no doubt come into contact with the membrane respiratory patches, and these will be affected in much the same fashion as the respiratory enzyme set-up of the mitochondria has been shown to be involved during *in vitro* experiments. Those molecules that succeed in penetrating the membrane now thread their way through the labyrinth of the cellular ground substance; they are directed towards various regions of the cell by obscure forces and according to unknown rules. Whether they loiter on the way or fall by the wayside into traps prepared for their destruction we do not know; indeed, the whole mysterious trek is one of pure conjecture and awaits the inspired investigator.

But sooner or later contact is made with the organelles and once again problems of surface membranes are faced, which are, we may guess, similar to those previously encountered. At any rate, things go wrong with the respiratory functions congregated in the mitochondria, and when a number of these are disturbed the overall effect on the cell is serious, for its machinery begins to run down. Imagine the confusion and chaos throughout the cell that ensues when all kinds of co-ordinated enzymic systems get out of hand. Little wonder is it that, sooner or later, cell structure begins to crumble as order fails, and that the innumerable interphases now fall into the ways of dead membranes. Deprived of energy supply, the mitochondrial dynamos run down, nuclear function falls into enigmatical confusion and no longer directs the future of the cell according to the primordial law. And so disintegration spreads, with cleavage and disruption of function from structure until the cell collapses and falls victim to its own forces of dismemberment.

More complex must be the scheme that directs contact between bacterial toxins and the cell, even though the outcome—degeneration and destruction—is the same as with other varieties of injury. I have shown that certain toxins such as *Cl. welchii* α toxin act in the first instance through a lecithinase which disrupts key centres in the cell membrane; indeed, the highly important target areas may get the worst of it, with disorganization of cellular reactions

to stimuli of many kinds. Other toxins seem to block processes concerned in the transmission of co-ordinating stimuli between groups of cells. This appears to be the case with the tetanus and botulinum toxins, which interfere seriously with the acetylcholine mechanism (Ambache *et al.*, 1948a, 1948b; Burgen *et al.*, 1949). In other instances, especially with the endotoxins now being disentangled from Gram-negative bacteria, cellular metabolic functions seem to be the foci of attack, but there is an appalling lack of information about these matters. Clearly we are on the threshold of a vast new world of cellular research from which we may gain rich treasure if we explore it critically and with imagination. The reward will include, I feel sure, progress not only in fundamental knowledge about life but in applied pathology, carrying with it new ideas about the recognition and treatment of disease no less than the forestalling of sickness.

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According to a report of an informal working party on the treatment and disposal of sewage sludge (H.M.S.O., 1954, price 2s. 6d. net), the efficient treatment and disposal of sewage sludges, together with the production of useful and valuable by-broducts, constitute the most difficult and costly work undertaken at sewage works. The report discusses five methods of disposing of sewage sludge. These are in the order in which they should generally be given consideration: (1) Disposal in a liquid state, preferably after digestion, as a method of manuring grasslands. (2) Disposal in a liquid state, preferably after digestion, to manure agricultural land for general purposes. (3) Failing the possibility of final disposal in liquid form, efforts should be made to obtain an end-product in some dry state suitable, preferably after maturing and pulverization, to form slow-acting manure for agricultural land. (4) A still drier product than the above can be made, but this entails the use of expensive equipment. (5) Favourable conditions, usually to be found in rural areas and small market towns, may exist for the method of disposing of liquid sludge by composting with other waste materials, generally separated from household refuse.

POTASSIUM-LOSING NEPHRITIS PRESENTING AS A CASE OF PERIODIC PARALYSIS

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Recent workers (Platt, 1950; Nickel *et al.*, 1953) have emphasized a tendency to urinary loss of electrolyte in renal failure in addition to the more familiar excess retention of end products of nitrogen metabolism. In some patients this electrolyte loss dominates the clinical picture, and in the last 10 years cases of both sodium and potassium deficiency as a result of renal disease have been reported. The type characterized by excess sodium loss was first described by Thorn *et al.* (1944) under the name of "salt-losing nephritis." Such cases have many features like Addison's disease, in that weight loss, hypotension, cachexia, and low serum sodium are present, often associated with some pigmentation of the skin. They differ in that there is no favourable response to deoxycortone or to cortisone, but only to liberal supplements of sodium chloride.

Potassium loss often does not produce such obvious clinical effects, and there is little doubt that many cases of potassium deficiency due to excess urinary loss have passed unrecognized. Brown *et al.* (1944) first described cases of periodic attacks of hypokalaemic paralysis or weakness as a result of renal tubular acidosis. More recently, hypokalaemic paralysis has been described in the de-Toni–Fanconi syndrome, of both the adult and the infantile types (Milne *et al.*, 1952; Bickel *et al.*, 1953). In this paper we describe metabolic studies of a case of chronic pyelonephritis with severe urinary potassium loss.

Case Report

The patient was a married negress aged 41. She had lived in Nigeria until 1953, when, during a visit to Great Britain, her illness was first diagnosed and treated. She had been in good health until 1944, when she suddenly felt her legs becoming heavy and weak. There was complete paralysis of the legs and soon afterwards of the arms, lasting for two weeks. Since then she has suffered from periodic attacks of weakness of the limbs lasting from 2 to 20 days before relief occurs. There has never been any paralysis of the muscles of deglutition, respiration, or phonation, nor any diplopia. The attacks come on about every three months and tend to be precipitated by exposure to cold. She has always felt reasonably well between the attacks, but there is usually some slight residual muscular weakness. Her last attack started whilst on air passage to Great Britain. She was admitted to another hospital in this country with complete paralysis of the legs and weakness of the arms. A diagnosis of hypokalaemic paralysis of unusual type was made, and she was transferred to Hammersmith Hospital for further study.

On inquiry it was found that she had had three episodes of dysuria and frequency of micturition associated with pyrexia in 1945, 1946, and 1947. For the last three years there had been polyuria with nocturnal frequency of micturition. There was no family history of any similar urinary or paralytic symptoms.

The patient was co-operative and healthy-looking. On first admission to hospital she was unable to move her legs

and the tendon reflexes were absent. There was considerable weakness of the arms, but she was able to move them, and the tendon reflexes were present. There was no impairment of sensation.

She was hypertensive (blood pressure 180/110), and there was slight cardiac enlargement with an apical presystolic triple rhythm. Chest radiographs revealed no pulmonary abnormality. Intravenous pyelography showed a defective concentration of the contrast medium, but no evidence of renal calculus, nephrocalcinosis, or hydronephrosis. The electrocardiogram (Fig. 1) showed changes typical of hypokalaemia. There was depression of the S–T segment, inversion of the T wave, and an upright U wave in the left precordial leads. After potassium supplements had been given for several days these abnormalities were still present, but reduced in degree. There had also been a considerable reduction of voltage of the QRS complex in all leads, a change which has been described by Bryant (1948) after the administration of potassium salts.

FIG. 1.—Electrocardiogram (lead V_5) before (left) and after potassium supplements.

The urine showed a constant albuminuria (2 g./l. Esbach). There was complete isosthenuria, specific gravity being fixed at 1011 despite fluid restriction. A catheter specimen of urine showed occasional erythrocytes and pus cells, but was sterile on culture. Blood urea ranged from 27 to 42 mg./100 ml. Urea clearance was 58 ml./minute, and endogenous creatinine clearance 65 ml./minute. The patient was unwilling to permit determination of inulin and para-amino hippurate clearances, but it is probable, from endogenous creatinine clearance figures, that her glomerular filtration rate was approximately 50% of normal.

Serum electrolyte values before and during treatment are given in Table I. There was no evidence of renal osteodystrophy, serum calcium was 9.0 mg./100 ml., serum inorganic phosphorus 3.4 mg./100 ml., and serum alkaline phosphatase 3.8 King–Armstrong units per 100 ml. Serum albumin was 2.9 g./100 ml. and serum globulin 4.8 g./100 ml. (electrophoretic values). The high globulin was due to increase of the beta- and gamma-globulin fractions. There was no evidence of steatorrhoea, over 97% of ingested fat being absorbed.

TABLE I.—*Serum Electrolyte Values During Treatment of a Case of Potassium-losing Nephritis*

Date	Sodium mEq/l.	Potassium mEq/l.	Chloride mEq/l.	Bicarbonate mEq/l.
In-patient:				
24/10/53 ..	145	1·4	87	47
26/10/53 ..		1·5		
30/10/53 ..	143	2·7	95	34
3/11/53 ..	140	2·8	105	30
11/11/53 ..		2·7		31
19/11/53 ..	140	2·9	104	29
Out-patient:				
7/12/53 to 22/3/54				
Mean value ..	145	3·3	100	30·5
Range ..	140–152	2·6–4·1	92–106	25–35

Potassium supplements were started on 27/10/53.

The urine was normally either slightly alkaline or neutral in reaction. After ingestion of 12 g. ammonium chloride in six hours the minimum urinary *p*H was 6.6, showing an inability to secrete an acid urine despite an adequate acidifying stimulus. A rapid rise of urinary *p*H to a maximal value of 8.0 occurred after the ingestion of 250 mg. of a carbonic anhydrase inhibitor (" diamox "), showing that there was some synthesis of hydrogen ion from carbonic acid by the distal tubular cells and that the particular tubular defect was not due to absence of renal carbonic anhydrase.

The diagnosis was clearly one of hypokalaemic periodic paralysis. Balance data showed a constant abnormal loss of potassium in the urine, and therefore a diagnosis of familial periodic paralysis could be excluded. Cushing's syndrome, which causes increased urinary potassium loss, could be excluded on clinical grounds. In addition, the plasma level of 17-hydroxycorticosteroids determined by the method of Bayliss and Steinbeck (1953) was normal, and chromatographic analysis of compounds E (cortisone) and F (hydrocortisone) in the urine by the method of Cope

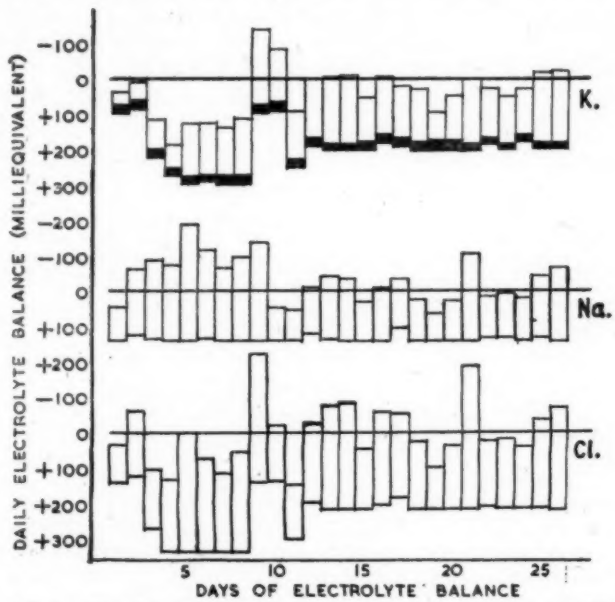

FIG. 2.—Electrolyte balance of case of potassium-losing nephritis during 26 days as an in-patient. Intake is plotted downwards from the baseline. Negative balance is recorded by the distance of each column above the base-line, and positive balance below this line. Black columns represent faecal excretion and open columns urinary excretion. Faecal sodium and chloride were negligible.

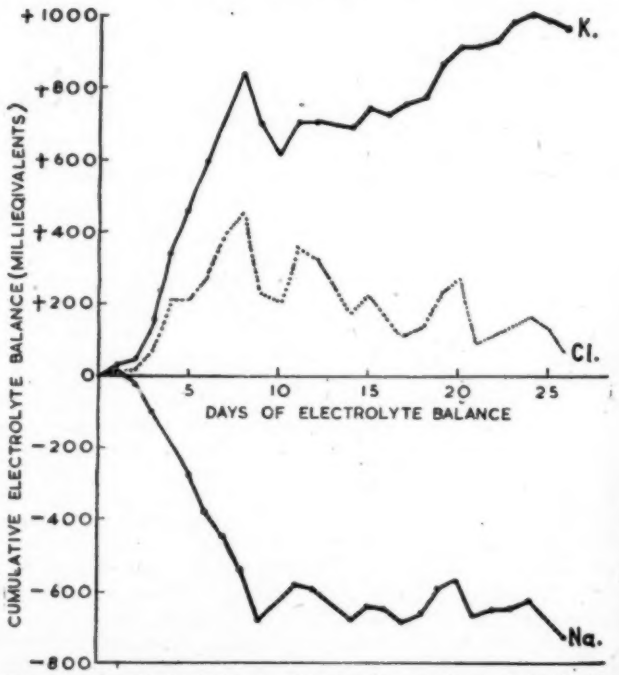

FIG. 3.—Cumulative balances of potassium, sodium, and chloride during the treatment of a case of potassium-losing nephritis with potassium supplements.

and Hurlock (1945) gave normal results. Bio-assay of electrocortin excretion by Cope and Garcia-Llaurado (1954), however, gave abnormally high figures. In view of the history and findings suggestive of chronic pyelonephritis it was thought that renal tubular damage was the cause of the hypokalaemia.

Balance Data.—The patient was put on a fixed standard diet containing 85 mEq of potassium and 140 mEq of sodium daily. Standard metabolic balance and analytical methods were used.

After a two-day preliminary period without potassium supplements, the patient was given 5 g. potassium chloride in water three times daily (200 mEq/day). In six days the patient retained almost 800 mEq of potassium and simultaneously lost over 500 mEq of sodium (Figs. 2 and 3). There was also a positive balance of chloride of more than 400 mEq. There was therefore excess retention of acidic over basic radicals with correction of the hypokalaemic alkalosis. On stopping the potassium supplements on days 9 and 10 the patient went into severe negative potassium balance, losing over 100 mEq potassium per day, despite the fact that the serum potassium had only risen to 2.8 mEq/l. and the electrocardiogram still showed unequivocal evidence of hypokalaemia. This confirmed that the potassium deficiency was due to grossly excessive urinary loss. The potassium clearance was now almost as high as that of endogenous creatinine, being 54 ml./minute, with ratio $C_k/C_{cr}=0.83$.

It now seemed undesirable to continue potassium supplements with this large dose of potassium chloride. The hypokalaemic alkalosis had been fully corrected before the potassium deficit had been completely restored. Continued dosage with pure potassium chloride would have caused a frank acidosis. A further complication arose from the isosthenuria. In Fig. 4 we show the relationship between the daily excreted osmotic load of solute and the daily urinary volume. The large dose of potassium chloride increased the urinary solute excretion from 800 to 1,375 m.osm. per day, with a consequent rise of urinary volume from 2 to 4.6 litres daily. The patient was therefore stabilized on a lower dosage of potassium salts, given as a mixture of 2 g. potassium chloride and 1 g. potassium citrate three times daily. On this regime the patient remained in slight positive potassium balance during the remainder of her stay in hospital, and the cumulative gain eventually exceeded 1,000 mEq of potassium (Fig. 3). There was no further gain or loss of sodium, but some excess chloride retained during the previous high chloride regime was gradually eliminated. There was no gain or loss of calcium or magnesium throughout, but during the period of maximal potassium retention a positive balance of 400 mg. of phosphorus occurred.

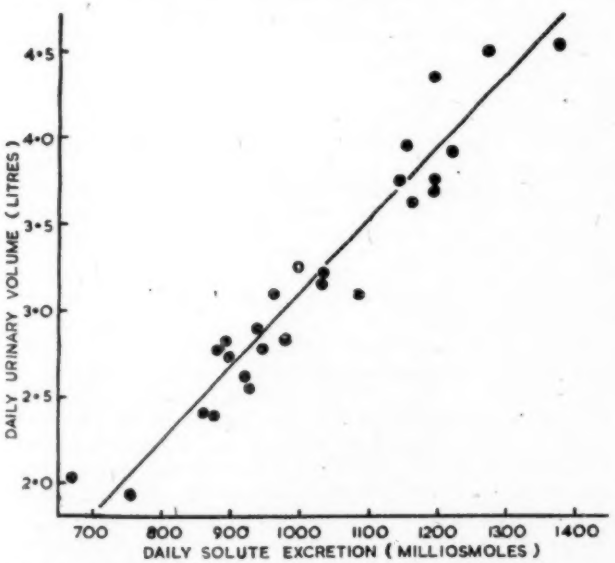

FIG. 4.—Relationship between the daily solute excretion and the daily urinary volume in the case of potassium-losing nephritis.

A control balance of 12 days' duration was observed in a normal subject (M.D.M.). After a three-day basal period, potassium chloride at a dosage of 15 g. (200 mEq) per day was taken in addition to a constant diet for six days. A three-day recovery period without added potassium salts was included (Fig. 5). The normal kidney was found to preserve almost perfect homoeostasis, very little biochemical change occurring. In Table II we compare the effects of six days on this high dosage of potassium chloride in the potassium-depleted patient and in the normal control.

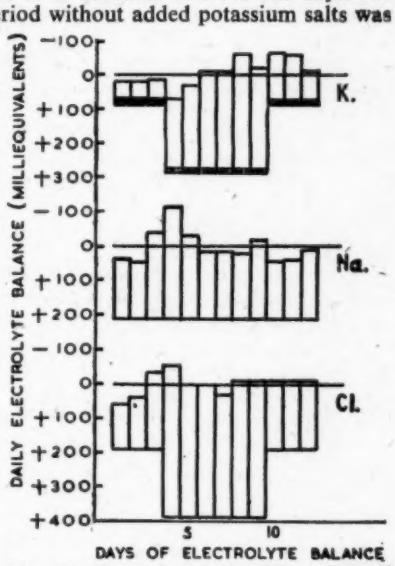

FIG. 5.—Electrolyte balance in a normal control subject. The presentation is similar to Fig. 2. From the fourth to the ninth day inclusive, 15 g. of potassium chloride was taken in addition to a standard fixed diet.

The patient was discharged from hospital in a state of moderate hypokalaemia with serum potassium averaging 2.8 mEq/l. The serum bicarbonate was within normal limits, and the average daily urinary volume was about 3,000 ml. Her muscular strength had much improved and the tendon reflexes of the legs were just present on reinforcement. The apical presystolic triple rhythm was no longer present.

TABLE II.—*Comparison of Biochemical Changes Induced by Daily Supplements of 15 g. Potassium Chloride in a Case of Potassium-losing Nephritis and a Normal Control Subject*

		Potassium-losing Nephritis	Normal Control
Serum potassium	Before K ..	1·5 mEq/l.	4·0 mEq/l.
	After K ..	2·8 „	4·4 „
Serum bicarbonate	Before K ..	47 „	28 „
	After K ..	30 „	28 „
Serum chloride	Before K ..	87 „	105 „
	After K ..	105 „	107 „
Clearance ratio (C_k/C_{cr})	Before K ..	27%	8·5%
	After K ..	83%	47%
Cumulative potassium balance ..		+796 mEq	+15 mEq
Cumulative sodium balance ..		−528 „	−125 „
Cumulative chloride balance ..		+446 „	+47 „
Cumulative phosphate balance ..		+5·5 m.mol.	+18 m.mol.

She has remained reasonably well during a period of four months' out-patient observation. There have been no further attacks of periodic paralysis, although some muscular weakness has sometimes been present. Supplements of 6 g. potassium chloride and 3 g. potassium citrate daily have in general been sufficient, but the dose has had to be increased for short periods when muscular weakness or hypokalaemia occurred. Serum electrolyte values during this period are summarized in Table I.

Discussion

The great majority of cases of excessive electrolyte loss in renal disease are secondary to chronic atrophic pyelonephritis. Evidence for this in relation to "salt-losing

nephritis" is discussed by Enticknap (1952). This case is probably one of the least complicated and most severe examples of potassium loss from pyelonephritis yet described. The balance data show that the total potassium deficit must have been greater than 1,000 mEq. Even after the patient had retained this amount of potassium there was unequivocal evidence of residual deficiency in that the serum potassium was still only 2.8 mEq/l., and the electrocardiogram showed the changes of hypokalaemia. In experimental potassium depletion (Black and Milne, 1952; Evans *et al.*, 1954), with deficiencies of about 300 mEq, the serum potassium level is of the order of 3.2 mEq/l. and any electrocardiographic change is slight and equivocal. It is likely, therefore, that the original total deficit of potassium in this patient was of the order of 1,500 mEq, which is just over 40% of her expected total body content of potassium. The balance data show that most of the intracellular potassium deficit had been replaced by a large increase of intracellular sodium. Approximately 70% potassium was replaced by sodium: this agrees well with the results obtained by Cooke *et al.* (1952) in potassium depletion in rats. The remainder of the potassium deficit is balanced by transfer of hydrogen ion from the extracellular to the intracellular phase, thus explaining the severe extracellular alkalosis found in this patient. Most of the retained chloride can be accounted for by the correction of this alkalosis. A positive phosphorus balance is almost invariable during the restoration of a potassium deficit. In this patient it was very small, and amounted to only 10 m.mols. of phosphate.

It is remarkable that this extreme degree of potassium deficiency should have caused such relatively mild symptoms. In the intervals between attacks of hypokalaemic paralysis this patient walked about normally and could undertake a full day's work. There was undoubtedly, however, great subjective and objective improvement in muscular power and in a general sense of well-being after partial restoration of the potassium deficit. Black and Milne (1952) have suggested that hypokalaemia associated with extracellular alkalosis causes less incapacity than a similar degree of potassium deficiency complicated by acidosis. Fourman (1954) considers that intracellular replacement of potassium by sodium may mitigate the effects of deficiency. This case seems to support these opinions. Also, potassium deficiency which has developed slowly over many years, as in this case, may probably be better compensated than the acute deficiencies seen after loss of gastro-intestinal secretions or in diabetic coma.

Usually, cases of potassium-losing nephritis are associated with acidosis either with or without renal rickets or osteomalacia (Brown *et al.*, 1944; Albright *et al.*, 1946; Milne *et al.*, 1952). Symptoms of hypokalaemic paralysis or weakness may then occur with less potassium deficit, and comparatively small supplements of potassium citrate are necessary in treatment. Only three cases similar to the one described here have been found in the literature. Earle *et al.* (1951) have described a patient with hypokalaemia from renal disease in whom the serum bicarbonate was normal, and the balance data suggest that there was a similar deficit of about 1,500 mEq of potassium. Unlike our patient, there was some tendency to a coincident sodium-losing state. Corcoran (1953) has briefly described an example of potassium-losing pyelonephritis with a normal glomerular filtration rate and with a potassium clearance almost equal to that of inulin. Wyngaarden *et al.* (1954) record a case with a similar renal lesion in which the potassium deficit was not so extreme but with a comparable degree of hypokalaemic alkalosis.

In general, there are two opposing factors which may influence the serum bicarbonate in renal tubular failure. The familiar acidosis of renal insufficiency lowers the serum bicarbonate, whilst abnormal loss of potassium tends to raise it owing to the development of hypokalaemic alkalosis. In the rare cases with extreme potassium loss, serum bicarbonate may be normal or considerably raised. Inability to form a normally acid urine in response to an adequate ammonium chloride load is more reliable proof of renal tubular acidosis than determination of serum bicarbonate, which may be influenced by a complicating potassium deficiency.

Explanation of the differential functional effects of chronic pyelonephritis can, in the present state of knowledge, only be speculative. Potassium loss in renal tubular acidosis has been claimed to be a part of the general loss of fixed base by a kidney denied the important base-conserving mechanism of ammonia synthesis (Albright *et al.*, 1946). This cannot be the explanation in this case, in which extreme potassium loss continued despite an alkaline urine and extracellular alkalosis when ammonia synthesis should be minimal. It is now considered that the most important renal mechanism for potassium excretion is a process of ionic exchange for sodium in the distal tubule (Berliner *et al.*, 1951). If this is accepted in the present case—and the very high C_K / C_{cr} clearance ratio makes such a mechanism likely—one is faced with the paradox that a destructive process has stimulated rather than depressed a normal urinary function. Selective inhibition or destruction of tubular enzyme systems will probably prove to be the reason for the diverse functional effects of pyelonephritis, and careful studies by histochemical techniques should be made if a similar case should come to necropsy. The tubular defect in this case was not due to absence of renal carbonic anhydrase, since inhibition of this enzyme resulted in a normal response.

The Differential Diagnosis of Periodic Paralysis

Periodic hypokalaemic paralysis secondary to renal disease is now easily distinguished from familial periodic paralysis in which there is no renal lesion. Points which are against a diagnosis of familial periodic paralysis in any given case are as follows:

(*a*) Lack of Family History.—Familial periodic paralysis is due to a dominant and usually non-lethal gene which does not interfere with reproductive fitness. The mutation rate of this gene must therefore be low (Haldane, 1935), and thus at least 80% of true cases of the disease give a positive family history.

(*b*) Late Age of Onset.—At least 60% of cases of true familial periodic paralysis start below the age of 16, while potassium-losing nephritis more often occurs in a later age group.

(*c*) Hypokalaemia and muscular weakness should not persist between the attacks of frank paralysis in familial periodic palsy, but usually do in potassium-losing nephritis. The interpretation of serum potassium levels should, however, always be made in relation to the serum bicarbonate. Acidosis tends to cause a higher serum potassium and most nephritic cases are acidotic.

(*d*) The attacks tend to be of longer duration and are more severe in potassium-losing nephritis. In familial periodic paralysis the longest duration of an attack with eventual recovery is that of a case described by Maclachlan (1932) in which paralysis on one occasion lasted for eight days. The case mortality from respiratory paralysis in the familial disease is given as 10% (Talbott, 1941). The true figure is probably lower than this, since some of the fatal cases have in fact been nephritic cases, incorrectly diagnosed as sporadic examples of familial periodic palsy.

(*e*) A diagnosis of familial periodic paralysis should be suspect if there is clear evidence of organic renal disease. Absence of albuminuria is not a sufficient criterion, since a normal result may be obtained in some cases of chronic pyelonephritis or the Fanconi syndrome. More delicate tests of tubular function such as the urine concentration test or the ability to acidify the urine should be included.

Accuracy of diagnosis is of more than academic importance. Larger potassium supplements may be necessary in the nephritic cases and the prognosis is more grave than that of the familial disease. Correct advice with regard to the hereditary aspects of a case of periodic palsy depends on diagnostic accuracy. Mistaken diagnoses are now uncommon, but were frequent before the metabolic cause of periodic paralysis was established by Aitken *et al.* (1937).

The following cases published as sporadic examples of familial periodic paralysis are thought, on the above criteria, more likely to have been cases of potassium-losing nephritis:

Maclaire (1925); Shinosaki (1926), one case; Vernon (1936); Poulsen (1938); Smith (1939)—first case.

Summary

A case is described of chronic pyelonephritis in which urinary potassium loss resulting in periodic hypokalaemic paralysis dominated the clinical picture. It was estimated by balance data that there was a deficiency of about 1,500 mEq of potassium, amounting to 40% of the total normal body potassium. The differential diagnosis betwen hypokalaemic paralysis of the familial type and that secondary to a renal defect is discussed. No explanation is given for the differential effects of chronic pyelonephritis on renal tubular function.

Thanks are expressed to Dr. R. J. Porter, who first diagnosed the case and arranged transfer to Hammersmith Hospital for balance studies; and to Dr. A. G. Macgregor for the out-patient data. We are indebted to Dr. R. I. S. Bayliss for determination of plasma 17-hydroxycorticosteroids and to Dr. C. L. Cope for determination of compounds E and F in the urine. Mrs. Walwyn-Jones and her staff gave invaluable assistance in supervising the various fixed diets in the balance studies.

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The Library of Congress has just published *Scientific and Technical Serial Publications, United States, 1950–1953*. This bibliography, which covers medical journals and reports, is divided into two sections, dealing respectively with non-government and government publications. Entries are grouped under a subject classification, and an alphabetic index of subject headings is included. Information is given regarding recent changes of titles, publisher, date of first issue, and frequency. The nature of the material included in each journal is indicated (for example, original research, review literature, abstracts, etc.). This work, which should be a useful addition to scientific bibliography, was prepared under the sponsorship of the National Scientific Foundation and can be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., price $1.25.

SIMILARITY OF SYMPTOMATOLOGY OF PREMENSTRUAL SYNDROME AND TOXAEMIA OF PREGNANCY AND THEIR RESPONSE TO PROGESTERONE*

BY

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An investigation was undertaken to ascertain the incidence of premenstrual syndrome in those who had previously suffered from toxaemia of pregnancy. This followed on the finding by Greene and Dalton (1953) of the high incidence of toxaemia of pregnancy (19%) among sufferers of premenstrual syndrome. The study of both diseases revealed a striking similarity of symptoms and signs suggesting a common aetiology. The successful treatment of premenstrual syndrome with progesterone (Gray, 1941; Puech, 1942; Albeaux-Fernet and Loublie, 1946; Greene and Dalton, 1953; and Rees, 1953a) suggested a possible treatment for toxaemia of pregnancy.

The investigation was carried out on 952 women, of whom 237 had suffered from toxaemia of pregnancy. Of these toxaemic mothers 40 were in the partnership practice and the remainder had been under the care of the local authority clinics, whose records were examined for the years 1942–53. Controls were women at a local engineering factory (614), and mothers with children under 5 years attending a routine infant welfare clinic (101). All were interviewed personally by me and set questions were asked. Those not already under treatment for premenstrual syndrome were given a special calendar on which to record the dates of menstruation and any recurrent symptoms during the six weeks immediately following the interview.

Premenstrual syndrome is often difficult to diagnose, for its recognition depends both on the intelligence of the patient and the severity of symptoms, so diagnosis was limited to those whose symptoms fulfilled the following conditions: (1) present in each of the three previous cycles, (2) severity sufficient to demand relief with analgesics or the seeking of medical advice, (3) occurrence at a specific phase of the menstrual cycle, confirmed by calendar and limited to the three premenstrual days, the period of menstruation, or mid-cycle. The diagnosis of toxaemia was limited to those who gave evidence of a blood pressure of 120/70 mm. Hg or below early in pregnancy, which rose after the 28th week to 140/90 mm. Hg or above, and for which treatment was instituted. Thirty-one cases of toxaemia of pregnancy were excluded owing to uncertain diagnosis or complicating factors—for example, pyelitis, placenta praevia; 96 women with no menstrual loss in the three previous months were excluded.

Results of Investigation

The results (Figs. 1 and 2) show the very high incidence of premenstrual syndrome in toxaemic mothers (86.4%), compared with controls (26.6%), and also show that the incidence of premenstrual syndrome increases in toxaemic mothers from 76.6% after one pregnancy to 100% after four pregnancies. Age had no apparent significance on the incidence.

The time of onset of premenstrual syndrome in toxaemic mothers was stated to be: puberty, 23%; following child-

*The Charles Oliver Hawthorne Prize essay, 1954.

birth, 34.9%; marriage, 2.3%; menopause, 2.9%; and unknown, 36%. While these times of onset may not necessarily be accurate, the fact that 26.2% of toxaemic mothers

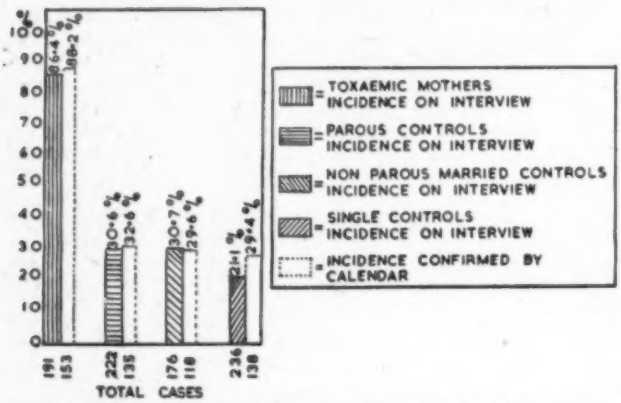

FIG. 1.—Incidence of premenstrual syndrome in toxaemic mothers and controls.

had premenstrual syndrome prior to the toxaemic pregnancy suggests that premenstrual syndrome cannot be regarded as the direct result of toxaemia; nevertheless the effect of a toxaemic pregnancy on an already established case of premenstrual syndrome is usually to increase the severity of the premenstrual symptoms. Graphs of the duration of an attack of premenstrual symptoms and also of its time relation to menstruation were found to show no significant difference between the type of attack experienced by the toxaemic mothers and the controls. The menstrual history of sufferers of premenstrual syndrome, whether toxaemic mothers or controls, was normal in regard to the time of first period, duration of loss, length of cycle, and absence of dysmenorrhoea, which confirms the finding of a normal menstrual history among sufferers of premenstrual syndrome reported by Rees (1953b) and Greene and Dalton (1953).

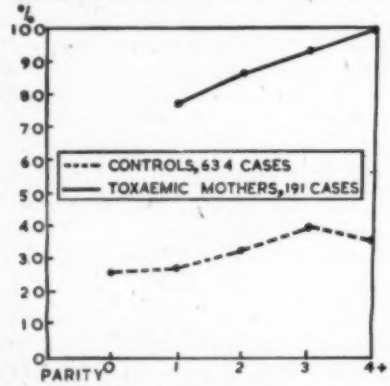

FIG. 2.—Effect of parity on incidence of premenstrual syndrome.

Minor Symptoms in Toxaemia of Pregnancy

Toxaemia of pregnancy is generally regarded as a disease without subjective symptoms, except prior to an eclamptic fit, therefore it was surprising at interview to find the toxaemic mothers describe minor symptoms, which had existed for many weeks or months before the development of signs of toxaemia. This was further confirmed by 92 mothers who had experienced both normal and toxaemic pregnancies; of these mothers 72 (78.3%) noticed the contrast between the sense of wellbeing and absence of symptoms in a normal pregnancy and the malaise and minor symptoms of the toxaemic pregnancy. These minor symptoms, which increase very gradually in severity and which may occur from early pregnancy onwards, include lassitude, hypersomnia, depression, nausea, irritability, headache, vertigo, visual aura, and ulcerative stomatitis, and are all symptoms of premenstrual syndrome. A marked similarity of symptoms in any one individual occurred during the toxaemic pregnancy and the premenstruum, and this was true whether the premenstrual syndrome had its onset before or after the toxaemic pregnancy. Thus, one woman, who recalled the left hemicranial headaches with "black snakes before her eyes" and ulcerative stomatitis during her toxaemic pregnancy, had since suffered from these same symptoms in the premenstruum. The following extract of a patient's letter also illustrates this similarity of symptoms:

Case 1.—A housewife aged 35 years, whose two pregnancies had been complicated by toxaemia, wrote: "My present trouble started with my first child, but still more so with the second. Roughly 15 days after the period I experience immediate and sudden pain, which forces me to retire unable to retain the straightened posture. This is preceded by a certain amount of white discharge. There is a feeling of being blown out with wind and frequency of passing water. The following day pain has gone but sensation of severe inflammation over entire part from waist down. There is backache, nausea, and complete exhaustion, and I feel really ill, rather as I did when in toxic conditions. Monthly periods completely free from all pain, but are rather slight." This patient became symptom-free on progesterone, 25 mg. alternate days, throughout the cycle and received a 500-mg. progesterone implant in June, 1953, which relieved the symptoms for eleven months.

The symptoms noted in toxaemic mothers during pregnancy and in the premenstruum are compared with the symptoms experienced by controls during the premenstruum in the accompanying Table.

Symptoms in Toxaemic Mothers in Pregnancy and Premenstruum and in Controls During Premenstruum

	Toxaemic Mothers		Controls
	Pregnancy*	Premenstruum	Premenstruum
	%	%	%
Headache	48·2	83·9	90·8
Vertigo	29·2	35·8	27·7
Nausea and vomiting	16·1	26·3	13·3
Visual aura	37·9	12·4	6·3
Lassitude	43·8	9·5	2·9
Depression	9·5	6·6	16·2
Irritability	13·8	10·9	9·2
Backache	5·8	13·8	6·3
Petit mal	1·5	0·7	0·6
Grand mal	5·8	2·2	†

* Excluding symptoms which ceased after the third month of pregnancy.
† Epileptics not eligible for employment at the factory from which most controls were interviewed.

It has been observed during pregnancy that when symptoms similar to those usually experienced in the premenstruum occur with increasing severity, pregnancy may culminate in abortion. It may be that some cases of abortion are due to early toxaemia of pregnancy and are thus analogous to the premature labour so frequent in toxaemia of pregnancy. The following case illustrates this:

Case 2.—A factory worker, aged 28, had progesterone treatment in February, 1952, for premenstrual syndrome, with symptoms of acne of face, nausea, lassitude, and depression, increasing during the premenstrual week and culminating in a headache over the right eye on the first day of menstruation. In May, 1952, she became pregnant and suffered increasing nausea, followed two weeks later by vomiting. At nine weeks she had a severe headache, which lasted seven days instead of the usual one day as in the premenstruum. The increasing severity of headache, vomiting, and photophobia forced her to rest in bed. Seven days after the onset of the headache she had a spontaneous abortion and all symptoms ceased.

Oedema, Hypertension, and Albuminuria in Premenstrual Syndrome

Day-to-day observations on several cases of premenstrual syndrome showed varying degrees of weight gain, oedema, hypertension, and albuminuria occurring during the premenstruum, as is illustrated by the following cases.

Case 3.—Childless housewife aged 40, suffering from premenstrual headaches, depression, and irritability. Albuminuria had been detected on many isolated occasions in the previous 11 years, but on investigation had been diagnosed as orthostatic albuminuria. Observations over two cycles showed the blood pressure to rise from 110/70 mm. Hg after menstruation to 140–160/80 mm. Hg in the premenstruum, and the albuminuria (in catheter specimens) was limited to the five premenstrual days. Treatment with 10 mg. of progesterone brought relief from all symptoms, blood pressure remained steady at 110/70 mm. Hg, and no albuminuria was detected during the menstrual cycles.

Case 4.—Childless housewife aged 42, suffering from premenstrual headache, depression, oedema, and dyspnoea. Observation revealed a weight gain of 11 lb. (5 kg.)—from 7 st. (44.5 kg.) after menstruation to 7 st. 11 lb. (49.5 kg.)—during the premenstruum—ankle circumference increased from 7¾ in. (19.7 cm.) to 9¾ in. (24.5 cm.), and albumin (3/1,000 Esbach) was present in the premenstruum. Moist sounds were heard in the bases of both lungs at the height of the oedema. Blood pressure was 200–250/120–130 mm. Hg throughout the cycle. When treated with 50 mg. of progesterone on alternate days she became symptom-free, her weight remained steady at 7 st. (44.5 kg.), ankle circumference fell to 7¼ in. (18.4 cm.), no albuminuria was detected, and no abnormal sounds were heard in the lungs. Blood pressure remained at 190–230/120–130 mm. Hg.

Case 5.—Club hostess, widow, aged 40, unemployed for six months owing to premenstrual epilepsy and bilious headaches. Her only pregnancy had been terminated at 28 weeks by caesarean section for chronic nephritis. The blood pressure rose from 120–130/80–110 mm. Hg during the postmenstruum to 190/110 mm. Hg immediately before a premenstrual epileptic fit, the weight rose from 9 st. 2 lb. (58 kg.) to 9 st. 6 lb. (60 kg.), and ankle circumference from 7¼ in. (19 cm.) to 8½ in. (21.6 cm.). Albumin (3–5/1,000 Esbach) was present throughout the cycle. When treated with 25 mg. of progesterone daily she became symptom-free, the blood pressure remained at 110/80 mm. Hg, weight steady at 9 st. 2 lb. (58 kg.), but albuminuria persisted at the same level.

These three cases can be recognized as analogous to the three classes found in toxaemia of pregnancy—namely, the commonest where, after a normal early pregnancy, there is a later development of toxaemic signs; those with hypertension in early pregnancy who later develop oedema and albuminuria; and those with albuminuria in early pregnancy who later develop hypertension and oedema. These cases also demonstrate the specificity of progesterone in acting only on those symptoms and abnormal signs present in the premenstruum, but not on abnormal signs present throughout the cycle. No previous studies have been traced of the occurrence of oedema, hypertension, or albuminuria limited to the premenstruum, nor of the specific action of progesterone in relieving these premenstrual signs.

Early Signs of Toxaemia

Cummings (1934) was the first to point out that the earliest sign of impending toxaemia is excessive weight gain in the middle trimester. Morton (1950), on the other hand, reported a definite weight gain in 52% of women suffering from premenstrual syndrome. Thomas (1933) reported two cases of massive oedema with weight gains of 8–12 lb. (3.6–5.4 kg.) coinciding with menstruation, and noted the subsequent diuresis accompanying the return to normal weight. Interest in these two cases is increased by the observation that one woman dated the onset of her condition to an eclamptic pregnancy and the other showed albuminuria at the height of the oedema. That the weight gain in both premenstrual syndrome and toxaemia of pregnancy is due to water retention is shown by the oliguria which accompanies the symptoms, and the spontaneous diuresis which occurs at the end (menstruation or labour), coinciding with a return to normal weight. Theobald (1950) has reported that in toxaemia the urinary output may exceed fluid intake by more than 6 litres in the second to fifth days of the puerperium, while Case 4 had gained 12 lb. (5.4 kg.) in the premenstruum, which she lost in two days by the diuresis she had always noticed to coincide with the onset of menstruation. It is well known that a copious flow of pale clear urine may mark the end of an acute attack of migraine or asthma.

Epilepsy in Relation to Eclampsia

There is no recognized relationship between an epileptic and eclamptic fit, although the character of the fit is identical; but Walshe (1952) noted that women show a special proneness to epileptic fits the day before menstruation; Dexter and Weiss (1941) have given a detailed account of the "unusual sequel" of idiopathic grand mal occurring after eclampsia; and Frohlich (1953) reported five cases of premenstrual epilepsy, in one of which the onset of epilepsy followed eclampsia. In the present investigation it was found that one eclamptic mother subsequently developed epilepsy, and of six pre-eclamptic mothers one subsequently developed grand mal and five had petit mal. In the following case epilepsy followed eclampsia and responded to ethisterone after 27 years' duration.

Case 6.—A housewife aged 63, gravida-5, had had her first and fourth pregnancies complicated by placenta praevia. Her fifth pregnancy occurred at the age of 36. She received no antenatal care, and at 37 weeks had seven eclamptic fits followed by the spontaneous delivery of a stillborn child. She recalled that this pregnancy had differed from previous ones in that she had felt ill throughout, and had suffered from severe headaches, preceded by an aura of black spots before her eyes. She is definite there was no oedema of ankles. She had since suffered from epilepsy and permanent right foot-drop. Fits occurred several times a week every three to four weeks and were worse at her periods. She had a normal menopause at 52 years, and since then several fits had occurred every two weeks. The fits resulted in complete loss of consciousness, were preceded by the same visual aura as noticed during her pregnancy, and were followed by severe headache lasting all day. When first seen in September, 1953, she was averaging six fits a fortnight in spite of phenobarbitone, 1 gr. (65 mg.) three times a day, and sodium phenytoin, 1.5 gr. (0.1 g.) three times a day. She had no albumin or oedema, and blood pressure varied between 160–140/110–90 mm. Hg. She was treated with ethisterone, 25 mg. three times a day, without any sedatives, and has reported no fits in the subsequent eight months.

This study has disclosed three stages in the development of both premenstrual syndrome and toxaemia of pregnancy. The earliest is the stage of minor symptoms, in which each individual's symptoms are of the same nature in the premenstruum and in pregnancy. As the disease advances, the stage of signs occurs with weight gain, oedema, hypertension, and albuminuria, and finally both diseases culminate in the stage of fits, either epileptic or eclamptic.

Treatment

In my practice 29 toxaemic mothers received treatment for premenstrual syndrome. Relief was obtained from progesterone injections in 18 cases and from ethisterone in the remaining 11. Six cases subsequently received a progesterone implant to provide prolonged action. These premenstrual symptoms, which were relieved by progesterone, were the same as occurred during toxaemia of pregnancy. In view of this common symptomatology a trial of progesterone therapy for toxaemia of pregnancy was undertaken.

Progesterone therapy in toxaemia was based on knowledge gained from its use in premenstrual syndrome. Experience has shown that for successful use progesterone must be administered before premenstrual symptoms begin, usually from the 14th to the 28th day, or throughout the cycle. Progesterone first administered during an acute attack of migraine, asthma, epilepsy, or depression will not lessen the symptoms or shorten the duration of attack, although, occasionally, rapid relief of premenstrual symptoms during an acute attack will follow the combined injection of progesterone, 25–50 mg., and mersalyl, 2 ml. It was found necessary to give progesterone in oil daily or on alternate days; larger doses did produce a longer duration of effect. Signs of overdosage of progesterone were euphoria, insomnia, restless energy, and dysmenorrhoea (which in pregnancy may resemble false labour). Severe overdosage may result in temporary faintness, sudden lowering of blood pressure, and muscular weakness of a myasthenic type. Progesterone may delay the onset of menstruation, and there is some evidence that it may also delay the onset of labour (Robson and Paterson, 1937). Deep intramuscular injections into the buttocks and avoidance of contamination of the outside of the needle with progesterone are necessary precautions to avoid urticarial weals from the presence of progesterone in the dermis. Ethisterone has the advantage of oral administration, but its dosage was found to be very variable. In some cases twice as much ethisterone was necessary to equal the effect of progesterone, sometimes a tenfold dose was required, but in others doses of

500 mg. of ethisterone daily were ineffective in bringing the relief which occurred with daily injections of 10 mg. of progesterone.

The scheme of progesterone therapy was formulated upon the recognition of the stage of minor symptoms preceding the development of toxaemic signs, and the belief that the severity of minor symptoms is related to the degree of progesterone deficiency. At routine antenatal visits patients were asked about the presence of nausea, headache, vertigo, and lethargy. If these or any other minor symptoms were reported an immediate injection of progesterone, 25–50 mg., was given, and the patient was seen again in three days. If symptomatic relief followed the test injection, that symptom was regarded as that patient's earliest indication of toxaemia, but if no relief followed some other cause for the symptom was sought. Minor symptoms were then treated with ethisterone, 10–250 mg. daily, or progesterone, 10–150 mg. daily or on alternate days, the dosage being raised until the patient was completely symptom-free, the interval between injections being gauged by the duration of relief following the test injection. Treatment was continued on a symptomatic basis, continuing while symptoms persisted and with an increase of dose if symptoms recurred. All patients were ambulant throughout and no dietary instructions were given.

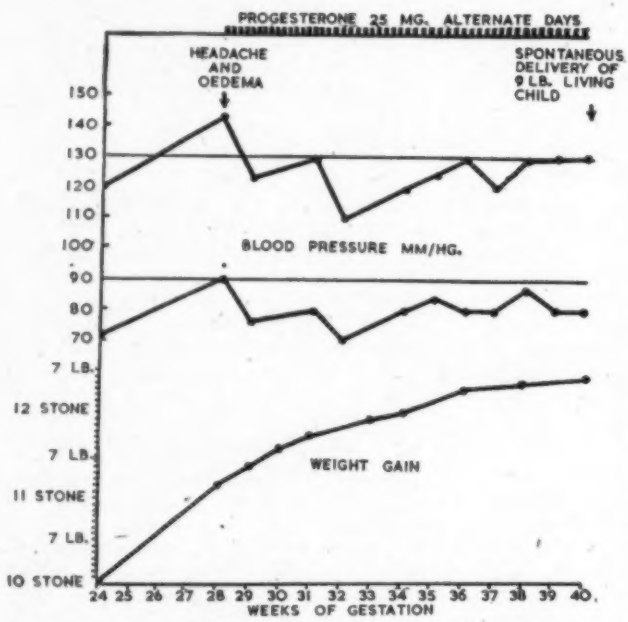

FIG. 3.—Case 7. Mild toxaemia treated with progesterone.

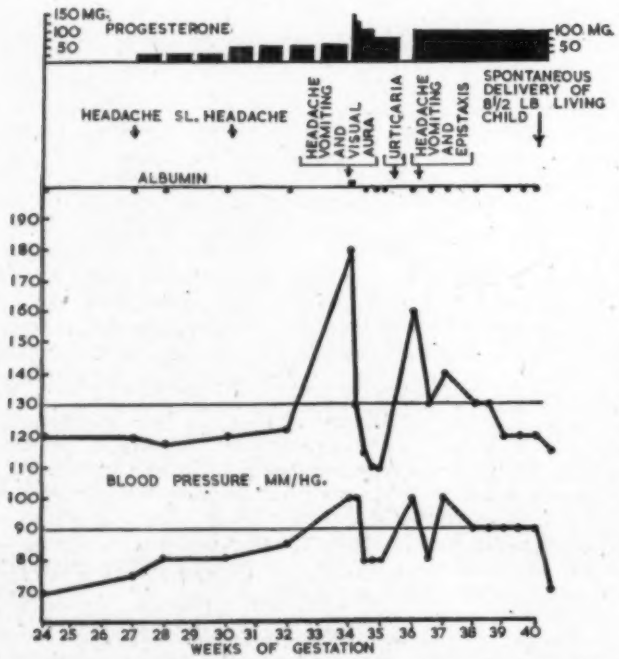

FIG. 4.—Case 8. Severe toxaemia treated with progesterone. The black dots below the albumin line indicate that no albumin was present.

Vomiting of early pregnancy was regarded as an early sign of toxaemia, for, while most cases cease spontaneously after the fourth month, it is recognized that many who continue vomiting throughout their pregnancy later develop toxaemia. Progesterone brought speedy and complete relief to 34 cases (100%) of vomiting of early pregnancy. Ten cases of moderate and one case of severe toxaemia have been treated on these principles, and all have gone successfully to full term without bed rest or surgical intervention and with the delivery of live babies. Cases 7 and 8 illustrate the use of progesterone in one case of moderate and one case of severe toxaemia (Figs. 3 and 4).

Case 7.—A housewife, aged 25 years, gravida-3, had had progesterone treatment for premenstrual syndrome with left hemicranial headache and lassitude, which followed her second pregnancy in 1950. In 1952 she became pregnant, with blood pressure 105–120/70 mm. Hg in the early months. At 28 weeks she complained of hemicranial headaches and bloatedness, had gained 16 lb. (7.3 kg.) in the previous four weeks, had oedema limited to the ankles, no albuminuria, and blood pressure of 145/90 mm. Hg. Progesterone, 25 mg., was given on alternate days. At 29 weeks she was symptom-free, had gained 3 lb. (1,360 g.) in one week, had slight oedema of ankles, and her blood pressure had fallen to 126/76 mm. Hg. The same dose of progesterone was continued throughout as she remained symptom-free. She had a spontaneous delivery at full term of a living child. (Fig. 3.) An extract of the pathologist's report of placenta read: "Cut surface shows spongy dark-red tissue throughout, with occasional small yellowish deposits of fibrin. Histology; normal placenta."

Case 8.—A housewife aged 35, gravida-2, developed toxaemia at 36 weeks during her first pregnancy and was admitted to hospital with a blood pressure of 180/110 mm. Hg. No improvement in hypertension or albuminuria with rest; surgical induction at 38 weeks. Uterine inertia in first stage and then a high forceps delivery of a living child. Duration of labour, 3 days 12 hours. Her second pregnancy, in 1953, began with blood pressure 120/70 mm. Hg. At 27 weeks she complained of lassitude, spots before her eyes, and nausea; no abnormal signs; obtained symptomatic relief for 24 hours following test dose of progesterone, 25 mg. She was given progesterone, 25 mg. daily, until the 30th week, when the dose was increased to 50 mg. daily for recurrence of headache. At 34 weeks she had a recurrence of severe headache with visual aura and vomiting. It was on a Monday, and the patient explained that symptoms were always worse on Mondays; for the nurse who gave daily injections did not come on Saturday or Sunday. She had oedema of ankles and face, a trace of albumin, and a blood pressure of 180/102 mm. Hg. She was given an immediate injection of progesterone, 150 mg., and mersalyl, 2 ml. The following day she felt better, and although the oedema was more marked her blood pressure had dropped to 130/100 and no albumin was present. Progesterone, 125 mg., was given. Two days later the oedema had disappeared, her blood pressure was 118/80, and she was completely symptom-free. She remained on a daily dose of progesterone, 75 mg., until the 36th week, when she developed an urticarial rash at the injection site. As she was completely symptom-free, injections were stopped for two days, but there was a recurrence of headache, vomiting, and epistaxis on the second injection-free day, and the patient was most anxious to return to injections. Her blood pressure had risen to 160/100, but there was no oedema or albuminuria. Progesterone, 100 mg., was then given daily until full term, when after a six-hour normal labour she produced a living 8¼-lb. (3.9-kg.) child. (Fig. 4.) The pathologist reported: "The maternal aspect is firm and brown, and cut surface shows spongy reddish tissue with a few yellowish areas suggesting fibrin deposition, not infarction. Histology: solitary infarct in one, and considerable fibrin deposition in fibrosing senile placenta."

This dramatic fall in blood pressure in Case 8 and improvement in general well-being in an ambulatory patient with severe toxaemia is of the type one associates with specific therapy.

Robson and Paterson (1937) demonstrated that convulsions, acute toxic conditions, and later death could be produced experimentally in rabbits during the latter half of pregnancy when they were deprived of the secretion of the luteal hormone or of gonadotropic hormone. They suggested that toxaemia in human pregnancy might also be associated with insufficiency of luteal secretion, and tested their hypothesis by treating 12 women suffering from severe toxaemia with daily doses of progesterone, 5 mg. for three to four days, and thereafter at longer intervals. They describe their results as encouraging. Clinical trials of progesterone were then undertaken by Marsden (1937), Young (1937), Paterson (1938–9), McMann (1938), and by Bennett, who in 1939, after reviewing all trials, concluded: "It is unlikely that progesterone treatment will ever find a permanent place in routine treatment of toxaemia."

In treatment of premenstrual syndrome it was found that the daily dose of 10–50 mg. of progesterone was necessary for symptomatic relief. The smallness of progesterone dosage in early trials might explain Bennett's conclusions, especially in view of Hoffmann and v. Làm's (1948) finding that in normal pregnant women at full term the progesterone level is raised some fifty times the normal non-pregnant value for the premenstruum. This suggests that, for complete progesterone substitution therapy, doses of 500 mg. or possibly even 2,500 mg. daily may be required. Dosages as high as 300–500 mg. daily have been used in non-pregnant women without side-effects in clinical trials on the value of various steroids in the treatment of rheumatoid arthritis (Copeman *et al.*, 1950). Thus Bennett's conclusion may be likened to the condemnation of insulin through its failure to relieve diabetic coma when used in a dose of less than one unit daily. It is also possible that progesterone substitution therapy should be started in the early stages of its deficiency and before the development of toxaemic signs.

The finding of low urinary oestrogen and pregnanediol output in toxaemic mothers by Smith and Smith (1938) led White (1947) to apply hormone substitution therapy to diabetic mothers, who are particularly prone to develop toxaemia of pregnancy. She gave stilboestrol and progesterone in daily doses of 5 mg. of each at 20 weeks, increasing to 30 mg. daily of each at term, and was able to claim a greatly lowered incidence of toxaemia. Oakley (1953), using similar hormone substitution therapy of the same dosage, but giving ethisterone instead of progesterone, was unable to report similar success. It has already been mentioned that ethisterone treatment of the premenstrual syndrome showed considerable individual variation in dosage requirements and results obtained in comparison with progesterone. Martindale (1952) states that the oral dose of ethisterone is approximately six times the injection dose of progesterone; therefore the substitution of ethisterone for progesterone at the same dosage cannot be expected to provide comparable results, and may explain Oakley's failure to repeat White's success.

Personal experience has shown that oestrogen administration increases the severity of premenstrual syndrome, thus confirming the findings of Israel (1938), and is to be expected if excessive oestrogen (Frank, 1931; Morton, 1950) or a high oestrogen–progesterone ratio (Israel, 1938; Greene and Dalton, 1953) is the cause of this syndrome. Oestrogens have been shown to produce oedema, clinically by Mazer and Israel (1951) and experimentally by Zuckerman and his colleagues (Krohn and Zuckerman, 1936; Aykroyd and Zuckerman, 1938; Zuckerman *et al.*, 1938) and by Gillman (1942). The similarity of the nausea of early pregnancy to the nausea induced by oestrogen administration was first noticed by Hirst (1918), and was confirmed by Finch (1942) and Patton (1949). Experimental work on rabbits has shown that the progestational effect of one unit of progesterone may be inhibited by 1/75th that amount of oestrone (Robson, 1947). Thus the use of stilboestrol combined with progesterone at equal dosage, as suggested by White in the prophylaxis of toxaemia, may be sufficient to inhibit the action of progesterone in the treatment of toxaemia.

Conclusion

From the foregoing the impression might be formed that toxaemia is an inevitable sequel to premenstrual syndrome, but Greene and Dalton (1953) reported that the incidence of toxaemia in their series was 19% and noted also that 62% of the women actually felt better than usual after the first trimester of pregnancy. During pregnancy the placenta provides an additional source of progesterone, which is produced in significant quantities after the end of the first trimester. Thus it is possible that in sufferers of premenstrual syndrome, if the placental production of progesterone is sufficient, no toxaemia will result, while if there is an excess of placental progesterone there will be a natural amelioration of recurrent symptoms. It was observed that many sufferers from premenstrual syndrome, who were symptom-free during pregnancy, made the significant remark when receiving progesterone: "I feel wonderful—just as if I were pregnant." On the other hand, should placental progesterone be insufficient at the time when the corpus luteum ceases to supply progesterone, a toxaemic pregnancy will result, unless the supply is made up from an extraneous source.

The corpus luteum is under the control of the gonadotropic hormone from the pituitary. Thus the progesterone deficiency of premenstrual syndrome may result from insufficient corpus luteal secretion or insufficient gonadotropic hormone; and the deficiency in toxaemia may result from insufficient gonadotropic hormone or insufficient placental progesterone. May it not be that a sufferer from premenstrual syndrome with progesterone deficiency resulting from corpus luteum may yet have sufficient gonadotropic hormone to stimulate, or even excessively stimulate, the placental production of progesterone? This would result in the natural alleviation of recurrent symptoms and the feeling of well-being during pregnancy as reported by Greene and Dalton in 62% of women suffering from premenstrual syndrome. Alternatively, where the progesterone deficiency is due to insufficient gonadotropic hormone, sufferers from premenstrual syndrome may also have insufficient stimulation from gonadotropic hormone to produce adequate placental progesterone, resulting in the development of toxaemia.

Summary

An investigation into the incidence of premenstrual syndrome in 952 women showed the high incidence of 86% among those who had suffered from toxaemia of pregnancy, compared with 26% in controls.

A stage of minor symptoms preceding the onset of toxaemic signs is reported, and these same symptoms tend to occur in the premenstruum.

Observations on women suffering from premenstrual syndrome showed presence of oedema, hypertension, and albuminuria in the premenstruum and the spontaneous disappearance of these symptoms with menstruation.

Both premenstrual syndrome and toxaemia of pregnancy appear to have three stages of development—a stage of symptoms, followed by signs (oedema, hypertension, and albuminuria), and culminating in fits, either epileptic or eclamptic.

Following the successful use of progesterone in premenstrual syndrome, a scheme of treatment for toxaemia is suggested, based on the recognition of the early symptomatic stage. The successful treatment with progesterone of 10 cases of moderate severity and one case of severe toxaemia are reported.

My thanks are due to Dr. Raymond Greene for his guidance and criticism; to Dr. Clunie Harvey and Dr. D. Regan for permission to examine antenatal records and arranging special clinics; to Mr. H. M. Rees for permission to interview toxaemic

mothers under his care; to Dr. J. G. Cunningham and his Directors for providing facilities for the study of factory controls; and to Dr. D. D. Reid for statistical assistance.

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REPORT ON THE USE OF GAMMA GLOBULIN AND ADULT SERUM FOR MEASLES PROPHYLAXIS IN ENGLAND AND WALES, 1949-53

BY

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Gamma globulin prepared by the method of Kekwick and Mackay (1954) was shown in a Report to the Medical Research Council (Report, 1950) on a series of controlled trials in day nurseries to be superior to adult serum for measles prophylaxis. Since 1949 gamma globulin produced on behalf of the Medical Research Council and Ministry of Health at the Lister Institute has been distributed, mainly for measles prophylaxis, by the Public Health Laboratory Service. It is issued in ampoules containing 250 mg. of protein, 96% of which is gamma globulin. The contents of each ampoule are derived from the fractionation of approximately 40 ml. human serum or about 48 ml. human plasma, and are dissolved in 3 ml. of sterile distilled water before injection.

During the same period irradiated adult serum—that is, serum from normal adults which has been exposed to ultra-violet light—has also been distributed for measles prophylaxis. Until February, 1951, the adult serum was issued at normal strength in 5-ml. or 10-ml. doses; thereafter it was concentrated to one-third its original volume, so that a 5-ml. ampoule contained the equivalent of 15 ml. of normal serum.

All doctors using the three prophylactics—gamma globulin, unconcentrated adult serum, and concentrated adult serum—were asked to complete a standard form reporting the results they obtained. During the period October 1, 1949, to December 31, 1953, report forms were returned for 82% of the 12,408 doses of globulin and 67% of the 3,931 doses of adult serum issued. These forms were analysed with three aims in view: (1) to obtain information on how measles prophylactics were used, so that the demand might be more satisfactorily met in future; (2) to determine the incidence of local and general reactions to inoculation; and (3) to gain some indication of the influence of dosage, the age of the person injected, and the period between exposure and inoculation on the prophylactic effect.

In the analysis all forms returned were used in the study of the distribution of measles prophylactics and of reactions to inoculation, but only those relating to 4,080 home contacts under 5 years of age were used to study the prophylactic effect. Full details of dosage and result were available for 3,846 of these, 2,760 of whom had received gamma globulin, 375 unconcentrated adult serum, and 711 concentrated adult serum.

Home contacts were selected because they were almost certainly exposed to infection, and if untreated most of them would have been attacked. The incidence of measles among susceptible children of different ages exposed to infection in another member of the same family has, in past studies, been remarkably constant. Family secondary attack rates noted by various observers are set out in Table I for children at different ages under 5 years and averages calculated from them. In the absence of any untreated but otherwise similar control group these average rates give the best available estimate of what might have been expected if no prophylactic had been used. On this basis about 9% of susceptible children under 6 months of age, about 70% over 6 months and under 1 year, about 88% over 1 year and under 3 years, and about 89% over 3 and under 5 years would have been expected to develop measles when exposed to another case in the same family.

As gamma globulin and adult serum were not allocated to contacts at random it is possible that those who received gamma globulin differed in some relevant respect from those who received adult serum. This should be borne in mind when the results with gamma globulin and adult serum are compared. It is also possible that if all the forms had been returned instead of 80% different results might have been obtained.

Distribution of Measles Prophylactics

In relation to population and to incidence of measles, London and the South-east of England received much more gamma globulin than other parts of the country. In London and the South-east about 10 contacts were inoculated for every 1,000 cases notified, compared with about 3 contacts for every 1,000 cases in other regions. Steps have now been taken to ensure a more uniform distribution throughout the country. Three-fifths of the gamma globulin was used in hospitals and two-fifths in general practice. These proportions were roughly reversed for adult serum. Of the gamma globulin used in general practice 77% was administered to children less than 3 years of age, so it is already being used in the main for young children, and little further

economy in this direction is possible; only in hospital was an appreciable amount of gamma globulin given to children over 3 years of age.

Reactions to Inoculation

Local and general reactions were recorded as nil, mild, moderate, or severe. Moderate or severe local reactions were noted in 0.3% of children given gamma globulin, 1.2% of children given concentrated adult serum, and 1.0% of children given unconcentrated adult serum. Moderate or severe general reactions were noted in 0.8% of children given gamma globulin, 0.9% given concentrated adult serum, and 1.4% given unconcentrated adult serum. The smaller volume of the gamma globulin dose may have been partly responsible for the relatively smaller incidence of reactions.

Several doctors added a brief description of the reactions which occurred. None was severe enough to cause any anxiety. Twenty-nine of the 76 moderate or severe general reactions following gamma globulin were described—11 as rash and coryza, 14 as fever, 2 as vomiting, 1 as abdominal pain, and 1 as vertigo. It was not possible to determine when these reactions occurred in relation to the time of injection, and some of these illnesses were possibly modified measles.

Results in Relation to Age of Contact and Dose

Prevention

Measles attack rates among home contacts of different ages under 5 years treated with varying doses of the three preparations are shown in Table II. At all ages over 6 months an increase in dose of gamma globulin was accompanied by a fall in attack rate, the dose required to produce a given level of protection rising with age. When these rates are compared with the secondary attack rates in Table I it will be seen that a marked reduction was produced by less than 2 ml. of gamma globulin in children over 6 months and under 1 year, by 2 to 4 ml. in children over 1 year and under 3 years, and by 4 to 8 ml. in children over 3 and under 5 years. The doses required to produce attack rates of about 25% were 2 to 4 ml. in children over 6 months and under 1 year, 4 to 8 ml. in those over 1 year and under 3 years, and more than 8 ml. for those over 3 and under 5 years.

Few babies under 6 months of age developed measles, but only about 9% would have been expected to do so. These rates are not comparable, however, because for the most part babies of this age are given a prophylactic injection only if their mothers are thought not to have had measles and, if untreated, the attack rate among them might have been higher than 9%. The proportion of children over 1 year and under 5 years of age who developed measles after being given adult serum, whatever the dose or preparation used, was hardly lower than would have been expected if they had not been treated. Adult serum appeared to have some protective value, however, for children over 6 months and under 1 year of age, of about the same order as the lowest dose of gamma globulin.

Modification

In Table III the results of analysis of the severity of measles in treated home contacts are shown. It is difficult to interpret these findings without knowing in what proportion of cases of measles in uninoculated children the disease is as mild as in those where modification was described as "good." Good modification was recorded in about three-quarters of cases given gamma globulin and in about half those given adult serum. The proportion of well-modified measles in those who received gamma globulin appeared to vary with the dose used. It is possible that adult serum modified some of the attacks, particularly in children under 1 year of age, but its effect in children between 1 and 5 years of age was clearly much less than that of gamma globulin. The proportions of children in different age groups in which measles was neither prevented nor well modified are set out in Table IV. Nine out of 10 children over 6 months and under 5 years of age exposed to measles in the home and given one bottle (250 mg.) of gamma globulin were protected completely or had only a mild attack.

TABLE I.—*Secondary Attack Rate of Measles Among Susceptible Family Contacts Under 5 Years of Age, According to Different Observers*

Age of Children at Risk	Butler (1912–13) in Willesden		Chapin (1925) in Providence, Rhode Island		Top (1938) in Detroit		Wilson *et al.* (1939) in Providence, Rhode Island		Stillerman and Thalhimer (1944) in New York		Average Attack Rates Based upon All Observers	
	No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)
Under 6 months	174	*10·2*	1,208	*47·0*	193	*45·6**	247	*7·3**	21	*19·0**	442	*9·0*
Over 6 months and under 1 year	209	*77·0*					245	*65·3**	30	*63·3**	484	*70·0*
1 year	242	*84·3*	958	*86·1*	194	*91·2**	490	*83·5*	43	*86·0*	4,087	*87·5*
2 years	248	*89·1*	1,084	*89·8*	257	*91·1**	545	*86·6*	26	*92·3*		
3 ,, ...	323	*90·1*	1,115	*88·4*	328	*93·9**	577	*86·3*	33	*87·9*	4,691	*88·6*
4 ,, ...	316	*83·2*	1,055	*89·5*	279	*91·4**	635	*87·4*	30	*83·3*		

* Rates calculated from published figures.

TABLE II.—*Effect of Dosage of Gamma Globulin and Adult Serum on the Measles Attack Rates in Home Contacts Under 5 Years of Age*

Prophylactic	Dose	Under 6 Months		Over 6 Months and Under 1 Year		Over 1 Year and Under 3 Years		Over 3 Years and Under 5 Years	
		No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)	No. at Risk	*Attack Rate* (%)
Gamma globulin	Less than 2 ml. ..	34	*3*	29	*34*	44	*70*	15	*67*
	More than 2 and less than 4 ml.	333	*10*	664	*25*	1,128	*55*	254	*64*
	More than 4 and less than 8 ml.	29	*3*	77	*10*	89	*29*	40	*50*
	More than 8 ml. ..	1	—	6	—	8	*25*	9	*22*
Unconcentrated adult serum	More than 3 and less than 9 ml.	18	*0*	23	*43*	67	*75*	36	*69*
	More than 9 ml ..	21	*0*	49	*35*	115	*80*	46	*70*
Concentrated adult serum	More than 3 and less than 9 ml.	96	*17*	162	*43*	339	*80*	109	*87*
	More than 9 ml. ..	0	—	3	—	2	—	0	—

TABLE III.—*Doctors' Estimate of Severity of Measles in Home Contacts Over 6 Months and Under 5 Years of Age.*

Prophylactic	Dose	Over 6 Months and Under 1 Year		Over 1 Year and Under 3 Years		Over 3 Years and Under 5 Years	
		No. of Cases of Measles	Percentage with Good Modification	No. of Cases of Measles	Percentage with Good Modification	No. of Cases of Measles	Percentage with Good Modification
Gamma globulin	Less than 2 ml. ..	10	*60*	31	*61*	10	*60*
	More than 2 and less than 4 ml.	163	*79*	626	*78*	163	*72*
	More than 4 and less than 8 ml.	8	*88*	26	*88*	20	*75*
	All doses	181	*78*	683	*77*	193	*72*
Unconcentrated adult serum	More than 3 and less than 9 ml.	10	*70*	50	*54*	25	*44*
	More than 9 ml. ..	17	*35*	92	*52*	32	*31*
Concentrated adult serum	More than 3 and less than 9 ml.	70	*63*	272	*42*	95	*32*
Concentrated and unconcentrated adult serum	All doses	97	*59*	414	*46*	152	*34*

TABLE IV.—*The Proportion of Home Contacts Under 5 Years of Age in Which Measles Was Neither Prevented nor Well Modified*

Prophylactic	Dose	Under 6 Months		Over 6 Months and Under 1 Year		Over 1 Year and Under 3 Years		Over 3 Years and Under 5 Years	
		No. at Risk	Percentage Neither Prevented Nor Well Modified	No. at Risk	Percentage Neither Prevented Nor Well Modified	No. at Risk	Percentage Neither Prevented Nor Well Modified	No. at Risk	Percentage Neither Prevented Nor Well Modified
Gamma globulin	Less than 2 ml. ..	34	*3*	29	*14*	44	*27*	15	*27*
	More than 2 and less than 4 ml.	333	*2*	664	*5*	1,128	*12*	254	*18*
	More than 4 and less than 8 ml.	29	*0*	77	*1*	89	*3*	40	*13*
Concentrated and unconcentrated adult serum	All doses	135	*3*	237	*17*	523	*43*	191	*53*

Interval between Exposure and Inoculation

It is generally believed that measles prophylactics should be given as soon as possible after exposure to infection and that if given more than six days after first contact complete prevention is unlikely. Report forms for 1,719 home contacts over 6 months and under 5 years of age who had received more than 2 ml. and less than 4 ml. of gamma globulin were used to investigate this question. Doctors were not asked to state the date of first exposure on the record form until December, 1950, and only forms completed since then were suitable for this analysis.

As the inoculated children were home contacts the date of first exposure was almost always the day of onset of prodromal symptoms—that is, about three days before the appearance of the rash in the primary case. The attack rates for children inoculated at varying times after first exposure are shown in Table V. The effect of delay was not apparent in those under 1 year, not great in those between 1 year and 3 years, but clearly present in those over 3 years of age. It is possible that higher dosage would have offset the effect of delay in older contacts, but sufficient information was not available to test this.

TABLE V.—*Relation of Attack Rate to Interval Between Exposure and Inoculation in Home Contacts Over 6 Months and Under 5 Years of Age Treated with More than 2 and Less than 4 ml. of Gamma Globulin*

Exposure to Inoculation. Time in Days	Age Group					
	Over 6 Mths and Under 1 Yr.		Over 1 Yr. and Under 3 Yrs.		Over 3 Yrs. and Under 5 Yrs.	
	At Risk	*Attack Rate (%)*	At Risk	*Attack Rate (%)*	At Risk	*Attack Rate (%)*
Under 3 days ..	51	*25*	84	*37*	17	*47*
Over 3 and under 6 days	315	*24*	473	*55*	113	*60*
Over 6 and under 9 days	196	*26*	322	*61*	57	*79*
Over 9 days ..	22	*18*	58	*55*	11	*91*
Total ..	584	*25*	937	*55*	198	*66*

Discussion

A report by Greenberg *et al.* (1944) on the results of the prophylactic effect of gamma globulin in children exposed to measles in their own homes can be compared with those in this study if allowance is made for differences in strength of the gamma globulin preparations used. Greenberg and his colleagues gave 2 ml. from a phial containing 2.2 ml., to allow for waste, to each of 814 household contacts aged more than 6 months and less than 6 years. Their preparation contained between 153 and 224 mg. of protein per ml., 85 to 99% of which was gamma globulin. Thus 2.2 ml. would have contained between 286 and 488 mg. of gamma globulin. Almost all children who received more than 4 ml. and less than 8 ml. in our study were given the contents, less wastage, of two bottles each containing about 240 mg. of gamma globulin—that is, 480 mg. in all. The measles attack rates in children who received over 4 ml. and less than 8 ml. in the three age groups, over 6 months and under 1 year, over 1 year and under 3 years, and over 3 and under 5 years, were in our series 10, 29, and 50% respectively: whereas the corresponding rates calculated from the figures of Greenberg *et al.* were 5, 21, and 31%. The rates in both series are of the same order, and though the American gamma globulin, despite rather lower dosage, appears to have given better results, this may be due to many factors other than differences in methods of manufacture.

The findings of Stokes *et al.* (1944) and Ordman *et al.* (1944), though very similar to those of Greenberg and his colleagues, cannot be compared with our figures because of differences in the age grouping.

In the doses used adult serum was clearly inferior to gamma globulin for both prevention and modification, and

in all age groups no better results were obtained with more than 3 ml. and less than 9 ml. of concentrated adult serum than with the same dose of unconcentrated serum. The poor protection obtained from unconcentrated adult serum is easily understood when the gamma globulin content of the small doses is considered. The doses most frequently employed, 5 ml. and 10 ml., contain only about 40 and 80 mg. of gamma globulin respectively. Though there have been many reports on the use of adult serum, only in one, that of Morales and Mandry (1930), were there records of results in more than a very small number of the inoculated children exposed to measles in another member of the same family. In that study 10 to 40 ml. of adult serum was given, and a steep rise in attack rate was observed with doses less than 20 ml. Insufficient details of age and dose were supplied for a direct comparison of their results with those in Table II. The degree of protection obtained, however, seemed to be of about the same order.

Though there was evidence in a previous report (Cockburn *et al.*, 1951) that gamma globulin was probably free from the risk of transmitting serum hepatitis, recent surveys carried out on behalf of the Ministry of Health, the Medical Research Council, and the Department of Health for Scotland (Report, 1954) have shown that exposure of plasma to ultra-violet light did not prevent subsequent cases of the disease. In view of this serious potential danger and of the small degree of protection obtained it would appear wise to abandon the use of pooled adult serum for measles prophylaxis. Convalescent measles serum is of well-established value, and, if taken from a single donor to minimize the risk of hepatitis, would seem to be the best alternative when gamma globulin cannot be obtained.

A Suggested Dosage Scale for Gamma Globulin

A scale of dosage based upon the results of this investigation is set out in Table VI. It aims at being simple, economical, and practical, and at providing good protection for the greatest possible number of children. Slightly greater protection could probably be obtained from higher dosage, but as the demand for gamma globulin exceeds the supply this would seem justifiable only in exceptional cases.

TABLE VI.—*A Suggested Dosage Scale for Gamma Globulin*

Aim	Age of Child		
	Under 1 Year	Over 1 Year and Under 3 Years	Over 3 Years
Prevention ..	3 ml. (250 mg.)	6 ml. (500 mg.)	9 ml. (750 mg.)
Modification ..	3 ml. (250 mg.)	3 ml. (250 mg.)	3 ml. (250 mg.)

The two scales, one for prevention and one for modification, suggest a more precise association between dosage and result than was actually demonstrated. In the younger age groups a high probability of modification is unfortunately accompanied by a substantial risk of preventing measles altogether.

The same modifying dose of 3 ml. (250 mg.) is at present recommended for all age groups. It should be sufficient to prevent measles or to ensure a mild attack in an infant less than 1 year old; the degree of protection of older children would be less, but so would be the need for it. It is possible that a smaller dose of gamma globulin would be effective in modifying the disease, and studies on this point are being planned.

As gamma globulin may be required in special circumstances for the protection of contacts of infective hepatitis, poliomyelitis, and other diseases the amount available for measles prophylaxis may be insufficient to meet all requests, and it should be used mainly for children suffering from an intercurrent illness and for children whose general health or environment indicates that a serious outcome may be expected from an attack. Babies under 6 months of age as a general rule seem to acquire no protection unless their mothers have no past history of measles or are suffering from the disease. In conjunction with other measures, gamma globulin has proved useful in preventing outbreaks in children's wards where a case of measles has occurred, and its use for this purpose seems justifiable. It is probably better to give a sufficiently large dose to prevent the disease to children occupying beds near the measles case than to give a small dose to all children in the ward.

Summary and Conclusions

The use of measles prophylactics in a series of cases is reported upon.

Confirmatory evidence was obtained of the superiority of gamma globulin over adult serum in measles prophylaxis.

Measles, though not invariably prevented by larger doses, was usually prevented or modified by relatively small doses of gamma globulin.

Within limits the prophylactic effect of gamma globulin varied directly in proportion to the dose used and inversely with the age of the child inoculated and the length of time between exposure and inoculation. The effect of delay between exposure and inoculation was not apparent in children under 1 year of age and was only slight in children between 1 year and 3 years of age.

The use of gamma globulin for measles prophylaxis should be restricted to weakly children or children suffering from an illness, to children living in bad home or institutional environments, and for preventing the spread of measles in children's wards in which a case occurs. It should only be given to babies under 6 months of age whose mothers have not had measles.

It is suggested that adult serum has not sufficient value in measles prophylaxis to justify the risk of serum hepatitis which its use entails.

We wish to thank those doctors in all parts of Britain who have so conscientiously completed the report forms sent to them with measles prophylactics.

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The Central Midwives Board last year was continually facing problems arising out of the increase in institutional confinements, according to its report for 1953–4. But, in view of statistical estimates of future population trends and the expected increase in women between 18 and 30 years old in 1961, the board thought it important to maintain a well-organized domiciliary service even if the service were underemployed for a year or two. The number of midwives on the Roll increased by 129 to 56,807 on March 31, 1954, and in the twelve months to January 31, 17,513 midwives notified their intention to practise—an increase of 42 over the previous year's figure.

LEUKAEMIA AND PREGNANCY

BY

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The occurrence of pregnancy in women suffering from leukaemia or the onset of this disease during pregnancy is rare, and in the latter instance the diagnosis may be overlooked. Leukaemia itself is not a common condition. During 1948 it was responsible for only 1.6% of all malignant growths in Scotland (Registrar-General, 1948). The figures for England and Wales were almost identical. When only 95 cases, sufficiently documented, can be collected from the world literature, it will be appreciated that few of us are likely to have personal experience of a significant number of patients. Knowledge of the subject has therefore to be derived from analytical reviews of small series of cases.

Grier and Richter (1939) were able to collect references to 75 cases of pregnancy and leukaemia. In a later and more extensive review of the world literature McGoldrick and Lapp (1943) collected references to 111 cases, in only 75 of which was the diagnosis sufficiently substantiated. They added one case of their own. The cases were classified according to the results of blood examination into acute and chronic types, as in Tables I and II. Of 31 cases of acute leukaemia in McGoldrick and Lapp's series, 17 were myelogenous, 9 lymphogenous, and 2 haemocytoblastic; 3 were unclassified. Chronic leukaemia accounted for 45 cases—42 myelogenous and 3 lymphogenous. Williams (1948) traced eight additional cases and described two cases personally known to him, one of which was of acute monocytic type and which was claimed by him to be the only instance of this variety recorded. His series included three cases of acute leukaemia—one lymphatic, one myeloid, and one monocytic—and seven cases of chronic myeloid type; whilst Li *et al.* (1947) recorded four cases of the chronic myeloid variety. Edwards and Freeth (1950) reported one case of chronic myeloid leukaemia.

Having had experience of one case (Case 1), I was prompted to search the records for the past twenty years of a general hospital and of a principal maternity hospital. Details of a further three cases were traced. In view of the relatively small number of cases reported in the literature and of the problems involved, it seems justifiable to record the details of these four cases.

Case Reports

Case 1.—A 4-para aged 25 was admitted to hospital in January, 1948, complaining of shortness of breath and swelling of the abdomen for eight months. Amenorrhoea had been present for three years. The spleen was enlarged. Blood examination revealed: Hb, 65% Sahli (9.1 g.%); red cells, 3,400,000 per c.mm.; white cells, 223,000 per c.mm. (blast cells 1%, myelocytes 44%, polymorphs 55%). A diagnosis of chronic myeloid leukaemia was made. Treatment with urethane orally was given up to a total dosage of 199 g., after which her white-cell count had fallen to 12,000 while the differential count revealed no blast cells and only 5.5% myelocytes. She was discharged from hospital feeling well. Nine months later she was admitted to a maternity hospital complaining of vaginal bleeding, and was found to have a full-time pregnancy, complicated by lateral placenta praevia and severe ante-partum haemorrhage. She was delivered of a full-time mature stillborn male child. Her white-cell count was now 350,000. During the post-partum period she required 8 pints (4.5 litres) of blood to counteract haemorrhage. The spleen was enlarged down to the umbilicus, blast cells were present in the peripheral blood, and myelocytes constituted 49% of the white blood cells. A second course of urethane was given orally, and after a total dosage of 51 g. the white-cell count fell to 20,000. She remained well for six months, by which time the white cells had increased to 380,000. The leukaemia then failed to respond to treatment and she died shortly afterwards.

Case 2.—A 2-para aged 23 was admitted to hospital in July, 1937, with a diagnosis of anaemia and splenomegaly.

TABLE I.—*Summary of 34 Cases of Acute Leukaemia Associated with Pregnancy*

	Leukaemia			Pregnancy				Maternal Deaths				Foetal Deaths		
				Diagnosed										
	Myeloid	Lymphatic	Others	Before	During	Full Time	Premature	During Pregnancy	During Parturition	Post-partum	% Total	Stillborn	Premature	% Total
McGoldrick and Lapp's review (1943)	17	9	5	2	29	9*	11*	4	5	22	100	9	3	60†
Williams (1948) ..	1	1	1	—	3	1	1	—	—	3	100	1	—	33·3
	18	10	6	2	32	10	12	4	5	25		10	3	

* Includes only non-interrupted pregnancies. † Excludes those embryos not surviving to the stage of viability.

TABLE II.—*Summary of 61 Cases of Chronic Leukaemia Associated with Pregnancy*

	Leukaemia		Pregnancy				Maternal Deaths				Foetal Deaths		
			Diagnosed										
	Myeloid	Lymphatic	Before	During	Full Time	Premature	During Pregnancy	During Parturition	Within 1 Year	% Total	Stillborn	Premature	% Total
McGoldrick and Lapp (1943)	1	—	1 (18/12)	—	1	—	—	—	—		1	—	
McGoldrick and Lapp's review (1943)	41	3	38 (51%) (1 yr.)	6	20*	10*	1	2	12	36·5	2	3	16·4†
Williams (1948) ..	1	—	1 (3/12)	—	1	—	—	—	—		—	—	
Williams' review (1948) ..	6	—	6	—	4	1	—	—	2	33·3	—	1	20·0
Li *et al.* (1947)	4	—	2 (3 yr.) (1 ,,)	2	3	1	—	—	?1		1	—	25·0
Edwards and Freeth (1950)	1	—	1 (2 ,,)	—	1	—	—	—	?		—	—	
Present series	4	—	2 (6·12) (3/12)	1+1 P.M.	3	1	—	1	3	100·0	1	Twins	60·0
	58	3	51	9	33	13	1	3	17		5	6	

* Includes only non-interrupted pregnancies. † Excludes those embryos not surviving to the stage of viability.

Examination of her blood revealed: Hb, 45% (Sahli); red cells, 3,010,000 per c.mm.; white cells, 580,000 per c.mm. Chronic myeloid leukaemia was diagnosed, and she was given a course of *x*-ray treatment, applied to the spleen. Over a period of three months, 1,700 r skin doses reduced the white-cell count to 23,000, and the spleen was no longer palpable. She was discharged from hospital feeling well. One year later she was found to be six months pregnant. Her last pregnancy had been three years previously. She was feeling well and her white-cell count was 44,000. She was delivered of a live full-time female child weighing 6 lb. (2.7 kg.). Haemorrhage was slight and the third stage of labour normal. The white blood cells then numbered 174,000. She developed a progressive anaemia and died in coma twenty-five days after delivery. Necropsy confirmed the diagnosis of chronic myeloid leukaemia.

Case 3.—A housewife aged 27 was referred to a maternity hospital during her second pregnancy in June, 1949, as her abdomen seemed larger than her 33 weeks' maturity would suggest. One year previously she aborted after eight weeks' gestation. A vertex presentation was confirmed, but her spleen was also felt to be enlarged, and examination of her blood revealed chronic myeloid leukaemia. The white-cell count was 200,000 per c.mm.; Hb, 53% Sahli (7.4 g.%); and red cells 3,700,000 per c.mm. Labour began four weeks later, a forceps delivery being necessary. Brisk haemorrhage occurred, and despite blood transfusion she died seven hours later. The child was full-time, alive, and healthy. Necropsy proved the cause of death to be pulmonary thrombosis, and chronic myeloid leukaemia was confirmed.

Case 4.—A 9-para aged 33 was admitted to a maternity hospital in November, 1934, complaining of frequency of micturition. She was 33 weeks pregnant. Her previous pregnancy had been in 1932. Blood examination revealed: Hb, 41%; red cells, 3,300,000 per c.mm. There was no record of her white-cell count. Two days later she delivered herself of premature twin boys, who died shortly afterwards. Labour was short and easy, but four days later the patient, after a transfusion of blood, became comatose and died. Necropsy revealed splenomegaly and hepatomegaly, and further examination showed the presence of chronic myeloid leukaemia. Bilateral pyelonephritis was also present.

Discussion

In discussing the problem of leukaemia and pregnancy, it is desirable to consider separately the acute and chronic forms of the disease. Tables I and II have therefore been prepared to facilitate comparison and clarify the issues involved.

Chronic myeloid leukaemia has the highest incidence of all the leukaemias during the child-bearing period, and is thus the type most often associated with pregnancy. It was responsible for 61% of the total of 95 cases now under review, including four cases reported above. As regards the relationship of leukaemia to parity, the acute type occurs mostly in primiparae, whereas the converse is found in the chronic type.

Effect of Leukaemia on the Gravid Woman

Acute Leukaemia.—In a total of 34 cases of acute leukaemia complicating pregnancy, only two were diagnosed before pregnancy began; the remainder were diagnosed mostly at seven months' gestation. The maternal mortality was 100%. This is not surprising, as the average life expectancy after the onset of acute leukaemia is stated to be from four to eight weeks (Whitby and Britton, 1946). Four patients died during pregnancy, five during parturition, and the remainder in the post-partum period; few survived longer than fourteen days. Post-partum haemorrhage was severe in five cases and fatal in two. Death was due to the direct effect of acute leukaemia in the other cases.

Chronic Leukaemia.—With regard to the 61 cases of chronic leukaemia, Cases 1 and 2 were diagnosed before the onset of pregnancy, as were 83.6% of the reviewed cases, while in the remainder, with one exception, the diagnosis was made during pregnancy. Case 3 was diagnosed after reference to hospital as a possible obstetrical abnormality; it was only when an enlarged spleen was palpated, in addition to a uterus of 33 weeks' gestation, that full blood examination was prompted and the diagnosis became clear. Case 4 demonstrates that it is not always easy to detect splenomegaly in the presence of a gravid uterus nearing its full-time size. Splenomegaly and leukaemia were not discovered until necropsy. Judging from the literature, this diagnostic difficulty does not seem to have been given any prominence.

In cases associated with chronic leukaemia one death occurred during pregnancy, three during parturition, and 17 were confirmed within one year of delivery. McGoldrick and Lapp (1943) found a maternal mortality of 36.5%. Excluding their series, the mortality of the remainder of the cases was 37.5%. Survival for a period of six months was attained in only one instance in my series (Case 1), and antileukaemic treatment was necessary to sustain reasonable health.

When pregnancy was not interrupted by election, and excluding abortions, there were 13 premature labours and 33 full-time gestations. This agrees with my experience in the present series. Apart from a variable degree of anaemia and swelling of the ankles, chronic leukaemia does not seem to complicate maternal health to a gross extent. Severe haemorrhage was recorded in four cases and was fatal in only one instance. In Case 1 placenta praevia was responsible for severe blood loss.

Effect on the Foetus

Acute Leukaemia.—McGoldrick and Lapp's series of 31 acute leukaemias yielded a foetal mortality of 60%. They stated that stillbirths were an important cause of the high mortality, but did not record a figure. In 23 acute cases sufficiently documented there were 13 foetal deaths, 10 being stillborn and 3 neonatal. Stillbirths were therefore responsible for 76.9% of the foetal mortality.

Chronic Leukaemia.—In chronic leukaemia, McGoldrick and Lapp quoted a foetal mortality of 16.4%. From the data they produced it is not possible to check this figure or to state the percentage for stillbirths or prematurity. Excluding the 41 cases of their review, and one abortion and one caesarean section reported by Williams (1948), of the remaining 15 cases of non-interrupted pregnancies, there were 3 stillborn, 3 premature (including twins of Case 4), and 10 live children. The foetal mortality rate is therefore 37.5%, and stillbirths and prematurity are each responsible for 50% of the mortality. Precautions directed to the factors known to be responsible for premature onset of labour may be expected to reduce the foetal mortality. McGoldrick and Lapp did not mention the incidence of abortion, either spontaneous or therapeutic. Excluding their series, but including their own case, there was one abortion in 16 chronic leukaemias, or 6.2%.

All authors are agreed that there is no evidence that leukaemia can be transmitted from mother to foetus. The placenta seems to act as an insuperable barrier to the leukaemic process.

Effect of Pregnancy on Leukaemia

Does pregnancy have a harmful effect on the course of leukaemia? As regards acute leukaemia, this runs its usual short course, and it cannot be said that pregnancy particularly accelerates the fatal issue. With chronic leukaemia it is difficult to give a precise answer. Because of the insidious onset it is hardly possible to state accurately when the disease first starts, and hence it is difficult to give figures for any possible effect pregnancy may have on its natural progress. The prognosis also depends on whether or not antileukaemic treatment is given, and on its success. The average duration of life, following the onset of symptoms in 259 cases of chronic myeloid leukaemia, uncomplicated by pregnancy, as reported by various writers and quoted by Wintrobe (1951), is 3.28 years. Only Li *et al.* (1947) give

figures from which it can be stated that two cases had chronic myeloid leukaemia for over three years, during which time pregnancy occurred. McGoldrick and Lapp found that 51.3% of cases had had chronic leukaemia for one year before the onset of pregnancy. Edwards and Freeth's (1950) patient had been known to be leukaemic two years before her pregnancy, but it is not reported how long she lived afterwards. The course of the leukaemia from onset to death in Cases 1 and 2 can only be estimated as two and a half years, and in Case 3 as two years.

Hofstein (1931) favours the theory that the prognosis for the mother becomes more unfavourable with each successive pregnancy, and that in the later stages of chronic leukaemia pregnancy is not well tolerated and should be terminated. If pregnancy occurs during the first two years of chronic leukaemia, he feels that there is a good chance of delivery at term without danger to the mother. Taussig (1936) states that in acute leukaemia there is little to be gained by termination of pregnancy and that it is hardly, if ever, justified, except in terminal cases in which the possibility of securing a viable child presents itself. Williams (1948) employed caesarean section in one case of chronic and one case of acute leukaemia with survival of the mothers and offspring. McGoldrick and Lapp came to the conclusion that most cases stand parturition well, only to collapse shortly afterwards, but that in many cases the course of the leukaemia is not greatly, if at all, affected by pregnancy. In some cases there is an acute exacerbation of the leukaemia. Cases 1 and 2 seem to belong to this category. In Case 1 the white-cell count increased from 12,000 to 350,000 per c.mm. during the course of pregnancy and myeloblasts had reappeared, while myelocytes had increased from 5.5% to 49%. Megaloblasts were also noted in the peripheral blood, a finding previously reported by Stone (1950). In Case 2 the white-cell count had risen from 44,000 per c.mm. at the sixth month of gestation to 174,000 per c.mm. at parturition, during which blood loss was small, yet death occurred twenty-five days later owing to severe anaemia, despite blood transfusion.

Leukaemia and Multiparity

The occurrence of two successive pregnancies during the course of a leukaemia is rare. For obvious reasons it does not arise in acute leukaemia. Cameron (1890) and others have reported cases of two pregnancies in the course of chronic leukaemia, despite the fact that necropsies have often shown leukaemic infiltrations of the ovaries and uterus. In a case reported by Williams (1948) the patient conceived a second time one year after the termination of her first gestation. Cases 1 and 3 were probably pregnant twice during the course of their disease; their previous pregnancies had terminated eight and six months, respectively, before the diagnosis of chronic leukaemia was made. This is well within the period of 1.24 years stated by Hoffman and Craver (1931), from a series of 500 cases of chronic leukaemia, to be the average duration of symptoms before diagnosis is made.

Treatment

McGoldrick and Lapp found that arsenic as Fowler's solution was the treatment most commonly prescribed, but the cases they traced belonged to the era before the more recent advances in therapy were known. Irradiation, by x rays or radium, of the spleen, thoracic spine, ribs, and sternum gives useful results and is still regarded by many as the most reliable treatment. Case 2 is an example of the response usually obtained. Irradiation of the pelvis is not now practised because of possible harmful effect on the foetus (Rolleston, 1930).

Edwards and Freeth (1950) treated their case satisfactorily with urethane. Case 1 made an excellent response to this drug on two occasions, not only in the lowering of the total number of leucocytes but also in the improvement of the differential count. A maintenance dose of urethane was not prescribed under out-patient conditions in view of the danger of agranulocytosis (*Lancet*, 1948). Li *et al.* (1947) treated three of their cases with radioactive phosphorus after parturition, and later also by irradiation.

Many cases require treatment for anaemia, and blood transfusion before parturition may be necessary. Undue post-partum haemorrhage also calls for transfusion, though this complication is apparently much less common than might be expected, there being only three instances of fatal haemorrhage due to acute and chronic leukaemia out of 75 cases.

Conclusion and Summary

The occurrence of pregnancy in leukaemic females is rare. The prospects for mother and child are better in the chronic than in the acute type. In all cases there is a significant incidence of premature labour, but haemorrhage, either ante- or post-partum, is not as common as may be thought. Most patients with chronic leukaemia survive pregnancy and parturition, but many collapse soon afterwards with the inevitable extension of the leukaemic process. Whether or not pregnancy should be interrupted will depend largely on the facts of the individual case, but in general it is the opinion of most writers that the shock of interruption is just as great as that of parturition, and therefore the pregnancy should be allowed to continue. Foetal mortality, though considerable, is moderate when one considers the relatively high occurrence of prematurity. Treatment of anaemia and antileukaemic measures will enhance the chance of foetal survival.

Four cases of chronic myeloid leukaemia associated with pregnancy are described. Two of the patients were probably pregnant twice during the course of the disease. Other series on the subject are summarized and shown in tabular form. The effects of leukaemia on the mother and foetus are discussed. The question of whether pregnancy has undesirable effects on leukaemia is debated. Attention is drawn to the difficulty which may arise in detecting splenomegaly in the presence of a gravid uterus.

I thank Dr. Douglas K. Adams for his advice and for permission to publish the report on Case 1, which was treated in the Western Infirmary, Glasgow. I am indebted to the medical staff of the Glasgow Royal Maternity and Women's Hospital for access to their records.

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In his annual report to the Swaffham Rural District Council Dr. R. N. C. McCURDY took the opportunity to discuss the public health aspects of the work which has been done to show that cancer of the lung is associated with cigarette smoking, and in this connexion he was critical of the Minister of Health's statement in Parliament last February that the time had not yet come when the Ministry should issue public warnings against smoking. According to newspaper accounts this criticism was described as " gibing at the Minister " at a recent meeting of the Swaffham Rural District Council, which refused to accept the report.

CONGENITAL MALARIA IN ENGLAND

BY

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There is now general agreement that the foetus can become infected by the transmission of malaria parasites across the placenta, although such an event is acknowledged to be very uncommon. It is particularly rare in native populations living in hyperendemic regions, where the incidence of congenital malaria is 0.03% against 1–4% in infants born to European mothers (Covell, 1950). An even higher percentage was recorded by Jones (1950), who found three cases of congenital falciparum (malignant tertian) malaria among 37 consecutive deliveries of non-African women at Lagos. Similar series have been reported from Albania and Italy. In Northern Europe, however, cases have been very scanty, and have usually arisen as a result of mothers with malaria coming home from the Tropics to have their babies. Only two cases were discovered in Belgium, both due to vivax (benign tertian) malaria; the first by Rodhain (1933) in a 9-weeks-old baby and the second by Glorieux (1952) in an infant 7 weeks old.

Three of the four cases so far described in this country were caused by *Plasmodium vivax*, the diagnosis being made at 16 days (Jones and Brown, 1924), 34 days (Gammie, 1944), and 50 days (Tanner and Hewlett, 1935) after birth. The one case of falciparum malaria was diagnosed at the age of 7 weeks by Moffat (1907).

The case of congenital malaria described below is the second to be reported in this country due to *P. falciparum*, and was diagnosed on the eighth day after birth.

Case Report

An Englishwoman aged 24 was first seen in the antenatal clinic of Queen Mary's Hospital, Stratford, London, when she was five months pregnant with her second child (the first was born uneventfully at Huddersfield). She gave her London address on registration, but, giving her history, omitted to mention she had come from Lagos, Nigeria, and that she had contracted her first attack of malaria one week before returning to this country by sea, with two possible mild relapses soon after her arrival here.

At her first examination her temperature was 99.4° F. (37.4° C.), pulse 98, and haemoglobin 68% (10.6 g.). Her blood pressure and urine were normal; Wassermann reaction and rhesus (Rh) factor negative. Her Hb averaged 60 to 65% throughout her pregnancy in spite of oral and intravenous iron, folic acid, and vitamin B_{12}. Agglutinins to D-antigen were consistently absent. Five weeks before delivery her Hb was 60% (8.9 g.), red cells 2,870,000 per c.mm., white cells 8,100 (polymorphs 73%, lymphocytes 23%, monocytes 3%, eosinophils 1%).

After a first stage lasting 4 hours 50 minutes, she was admitted on November 13, 1952, in the second stage of labour, which lasted only seven minutes. She was passing a lot of liquor amnii heavily stained with meconium, and the foetal heart sounds were not heard. The baby, which was full-term, was delivered under gas-and-air analgesia. The placenta, battledore in type and weighing 1 lb. 7¼ oz. (0.68 kg.), was delivered 13 minutes later and found to be ragged and infarcted with ragged and ? incomplete membranes. At the end of labour the mother's temperature was 97.6° F. (36.4° C.), pulse 76, respiration 18, and blood pressure 110/70.

The infant, a female weighing 6 lb. 11½ oz. (3.05 kg.), was very blue at birth, but cried after two minutes. The cord blood was Rh positive and the Coombs test was negative. The temperature of the baby taken routinely soon after birth was 96.6° F. (35.9° C.).

Opinions differed on when jaundice first appeared; one house officer and a midwife thought a "few hours" after birth, while another house officer and a second midwife were certain it was present 30 hours after delivery, when the baby attracted attention to itself by a twitching of the lips, chin, and hands. Unfortunately the temperature was not taken at this juncture, and it is therefore impossible to decide in retrospect whether this twitching was caused by cerebral irritation due to precipitate labour and asphyxia neonatorum, or whether it was caused by a paroxysm of fever. When I first saw this baby, 44 hours after birth, the jaundice was intense and of the colour one associates with icterus gravis. The head was retracted without bulging of the anterior fontanelle, the liver was one fingerbreadth and the spleen two fingerbreadths enlarged below the costal margin, urine dark, temperature 100° F. (37.8° C.), and respirations 55. Vomiting occurred after some feeds. The Hb was 110% (16.3 g.).

The diagnosis was in doubt, but it was felt that congenital infective hepatitis was a possibility. Examination of the mother's blood, which showed a thymol turbidity of 6 units and colloidal gold of 4 units, seemed to confirm this clinical impression.

Fourth Day (November 16).—Jaundice and head retraction were still very marked, with, in addition, moderate dehydration. The temperature was 102° F. (38.9° C.) and respirations 88. The serum thymol turbidity was 3 units and blood culture was sterile. The cerebrospinal fluid was also sterile, but blood-stained, containing 27,000 red cells and 111 white cells per c.mm., of which 44 were polymorphs and 64 were lymphocytes. The urine contained epithelial cells and bilirubin crystals with a trace of albumin: Fouchet's test for bile pigments was strongly positive and Hay's test for bile salts was negative. In view of the serious condition of the baby, aureomycin, 250 mg. every six hours, was given by mouth, together with vitamin K and methionine; subcutaneous N/2 saline was also given.

Fifth Day.—The maximum temperature recorded was 102.8° F. (39.3° C.) and respirations 56. There was no change in the infant's condition.

Sixth Day.—The liver was three fingerbreadths and the spleen two fingerbreadths enlarged. Jaundice and head retraction were unchanged, but the maximum temperature was only 99.8° F. (37.7° C.) and respirations 46. The cerebrospinal fluid now contained 4,600 red cells and 52 white cells per c.mm. (47 polymorphs, 5 lymphocytes). This was the third day on aureomycin and slight improvement only had been made.

Eighth Day.—A chance remark by the ward sister to the effect that the baby was a precious one, since the mother had come all the way from Africa to have it, made one think immediately of congenital malaria. The infant's thin blood film was negative, but the thick drop preparation showed scanty *P. falciparum* (malignant tertian) rings, while the mother's blood films, both thick and thin, showed the same species of parasite but in greater numbers. The baby's white cell count was 21,000 per c.mm. (polymorphs 50%, lymphocytes 37%, monocytes 11%, and metamyelocytes 2%); dark pigment granules were present in some of the monocytes. The haemoglobin was 90% (13.3 g.).

Although the infant was by now apyrexial, its condition was unsatisfactory. Jaundice was still intense, head retraction marked, and hepato-splenomegaly pronounced. Aureomycin was stopped as soon as malaria was diagnosed, and mepacrine, ¼ tablet (0.05 g.), was given three times a day. Four doses in all were given, but vomiting was excessive, and it was felt that little was being absorbed. Pyrimethamine ("daraprim") was therefore obtained.

Tenth Day.—Pyrimethamine, ¼ tablet (6 mg.), was given by mouth and repeated on the following day. The baby vomited twice on the first day, but not at all on the next day. The head retraction thereafter was no longer noticeable and the jaundice began to lessen, with the liver now

two fingerbreadths and the spleen one and a half fingerbreadths enlarged. The urine contained very few bilirubin crystals and no methaemoglobin or urobilinogen, but Fouchet's test was still strongly positive. Schumm's test for methaemalbuminaemia was negative, the van den Bergh reaction direct positive, icterus index approximately 50 units, and thymol turbidity 2 units. The thick drop preparation became negative for malaria parasites from the time antimalarial therapy was instituted.

Fourteenth Day.—The haemoglobin was only 64% (9.47 g.), and therefore iron and vitamin C were prescribed. The infant's general condition was greatly improved despite continuing jaundice and biliuria. The liver was only one and a half fingerbreadths and the spleen one fingerbreadth enlarged.

Eighteenth Day.—The mother, who had meanwhile been successfully treated with mepacrine and proguanil, was able to take her infant home to Huddersfield, albeit still mildly jaundiced but weighing 6 lb. 3½ oz. (2.84 kg.) and gaining weight on the breast.

Later Progress.—The baby was readmitted to hospital on January 10, 1953, when 8½ weeks old, because, while away from London, she had been lethargic for at least a week and very slow in taking the breast, although fed every three hours. There had been a cough for five days before admission. On examination she was cachectic, with an earthy complexion and dry skin, and was alarmingly underweight, weighing only 5 lb. 11½ oz. (2.6 kg.). The lungs were full of crepitations, but the temperature and respiration rate were normal. *X*-ray examination showed the appearances of patchy collapse at both bases. Jaundice was absent, but the liver was two fingerbreadths and the spleen one fingerbreadth enlarged below the costal margin. The Hb was 86% (12.73 g.) and white cells 20,000 per c.mm. (77% polymorphs). No parasites were seen in either the thick or the thin films. The urine contained no bile salts or pigment and the total serum bilirubin was 0.9 mg. per 100 ml. In spite of the negative blood films a malarial relapse was considered possible, and pyrimethamine was again given (¼ tablet daily for two days), together with oxygen, penicillin, and aureomycin. It is of interest to note that four days after admission there was an eosinophilia (of 12%), which McGregor and Smith (1952) have recorded after the administration of pyrimethamine, and the Hb at the same time was only 69% (9.6 g.). Weight gain was rapid, and on discharge from hospital, on February 7, at the age of 12½ weeks the infant weighed 7½ lb. (3.4 kg.), her spleen was only just palpable, and the liver no longer felt.

A month later the mother returned with her baby to Apapa, near Lagos, where she had resided for a year.

Diagnosis

Before it was known that the mother had come from Lagos, the newborn infant was suspected of suffering from congenital infective hepatitis, and this diagnosis seemed to be confirmed by the mother's liver-function tests. The vital information that the mother had become pregnant in West Africa was not revealed until the baby was 8 days old. The correct diagnosis then became clear, because war experience in the Tropics has shown how often malarial jaundice can be confused with infective hepatitis until a blood examination for parasites has been made.

The features of jaundice, head retraction, and dyspnoea do not necessarily make the case one of cerebral malaria, because (1) head retraction could well be attributed to cerebral irritation following asphyxia neonatorum and precipitate labour, although it disappeared after pyrimethamine was given; (2) the pleocytosis of the second sample of cerebrospinal fluid could have been due to traumatic haemorrhage when the first sample was taken; and (3) cerebral symptoms often occur in malaria of the young and therefore cerebral malaria is very difficult to diagnose (Williams, 1940). The intense dyspnoea of the infant at the outset is of interest, as, although emphasized in small children by Jemma (1936) and Bergeret (1948), it has been ignored in case reports of congenital malaria. It is of some importance, since differentiation from pneumonia may not be easy.

Whereas diagnosis in the neonatal period is not difficult once malaria has been called to mind, the clinical picture presented a few weeks or months later is quite different. The baby is then anaemic and dehydrated, with an earthy complexion, slate-grey cyanosis, cold extremities, oedema, basal rales, and failure to thrive. The liver and spleen are usually enlarged, but jaundice is rare; fever is sometimes high, but is more often absent, or the temperature is subnormal. This description is strikingly similar to the infant's condition when it was admitted to hospital at the age of 8½ weeks. There was neither fever nor dyspnoea, and the general appearance, earthy dry skin, and pallor were out of proportion to the signs in the chest. Although a malarial relapse appeared likely, no parasites were found in the blood, and so, although treatment with pyrimethamine and antibiotics was successful, the diagnosis must remain unestablished.

Treatment

When the original diagnosis of infective hepatitis was made, aureomycin was given on empirical grounds, and it is probable that, as a result, the infant's life was prolonged sufficiently for it to be saved by the antimalarial treatment subsequently given.

Aureomycin has been found to be therapeutically active against plasmodium infections in animals, but in human experiments its action was found to be too delayed to be of value as a curative agent (Cooper *et al.*, 1949). Nevertheless, Ruiz-Sanchez *et al.* (1951) claimed good results clinically, but found cure was slower than with routine antimalarial drugs. In our case, over the four days aureomycin was given, fever and dyspnoea slowly subsided, and just before mepacrine was substituted scanty falciparum parasites were found in the thick-drop film, confirming the definite but poor therapeutic action of aureomycin.

Mepacrine was not given by intramuscular injection, because of the alarming fits and even deaths recorded in infants and small children by Bruce-Chwatt and Bruce-Chwatt (1950), Jones (1950), and Dockeray (1951). It was administered orally in a dosage of 50 mg. thrice daily, but vomiting was too frequent. It is possible that the dose should not have exceeded 50 mg. a day. Reports of pyrimethamine were at that time so encouraging that after only four doses of mepacrine this drug was substituted.

Pyrimethamine had been reported effective in treating falciparum infections in Lagos school-children by Archibald (1951) even when as little as 5 mg. was given, but Bruce-Chwatt and Archibald (1953) found that single 25-mg. tablets were more effective in quickly abolishing falciparum parasitaemia. The use of a quarter of a 25-mg. tablet on two successive days produced no vomiting on the second day, and only twice on the first day, at times unrelated to the ingestion of the drug. No vomiting occurred when the second course was given 7½ weeks later. This is a tribute to its non-toxicity, which has been remarked upon by many who have used it—for example, Avery Jones (1952), who found it successful and without ill effects in seven infants aged between 3 and 12 months who were suffering from heavy falciparum malaria and who were given single doses of 5 to 10 mg. each. On the other hand, Goodwin (1952) has reported slight gastro-intestinal disturbance in two individuals, while Schmidt and Genther (1953) have struck a warning note as a result of experiments on monkeys which indicate that the drug may constitute a potential hazard to the human user. Some recent reports tend to show that pyrimethamine is not as effective a curative agent in malaria as some of the older established remedies. Further work is still required to establish its precise place in antimalarial therapeutics.

Summary

A case of congenital falciparum (malignant tertian) malaria is described which, by virtue of the intense jaundice, hepato-splenomegaly, and head retraction

produced, was thought at first to be due to infective hepatitis. The correct diagnosis became apparent when, on the eighth day after birth, it was learnt that the mother, an Englishwoman, had come home during her pregnancy from Lagos, Nigeria.

It is considered that aureomycin, given before the case was correctly diagnosed, kept the infant alive until more active antimalarial treatment could be adopted.

Mepacrine was given only a short trial, to be followed by pyrimethamine, which proved successful and non-toxic in the dose given. It is possible, but unproved, that 50 days later there was a malarial relapse.

The antimalarial actions of aureomycin and pyrimethamine as curative agents are briefly discussed.

My thanks are due to Dr. M. S. Ross for his pathological investigations, to Mr. B. G. Spiers for allowing me to have access to the antenatal and labour notes, and to Dr. A. C. Doyne Bell for his kind co-operation.

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THE VALUE OF RADIOLOGY IN ANTE-PARTUM HAEMORRHAGE

BY

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Location of the placental site by plain radiography was first described by Snow and Powell (1934), and later amplified by Dippel and Brown (1940) and Bishop (1945) in the U.S.A.; but the method had not had an adequate trial in Great Britain until Reid (1949) and Stallworthy (1951) gave an account of how radiological location of the placenta had been applied to the management of ante-partum haemorrhage.

This paper describes the results obtained in the use of radiography in determining the placental site in cases of ante-partum haemorrhage admitted to the Royal Hampshire County Hospital during 1951–3, and how these results have been applied.

Radiological Technique

The radiological technique follows closely that described by Reid (1949) and Whitehead (1953a); but special filters have not been used and the radiographs were taken on standard equipment supplied to all *x*-ray departments in general hospitals.

When it is decided that the patient is fit for the examination, she empties her bladder and rectum in the ward, and the following views are taken in the *x*-ray department: (1) lateral views of the abdomen in the recumbent position: one penetrated film for the posterior half of the abdomen, and a "soft" film for the anterior half; (2) a lateral view of the pelvis in the erect or semi-erect position. In a large proportion of cases these two views are sufficient to demonstrate the placental site, since it is usually on the anterior or posterior wall; but when the placenta is entirely or mainly on the lateral wall two additional views are required: (3) antero-posterior or postero-anterior films of the abdomen in the erect position; and (4) oblique films of the abdomen in the recumbent position.

Interpretation of the Radiographs

(*a*) *Normal Implantation of Placenta.*—A placenta implanted in the upper uterine segment can be seen in the lateral radiographs of the abdomen by tracing the uterine and foetal outlines, and noting where an apparent thickening occurs between the two outlines. This "placental shadow" varies in thickness between 3.1 and 5.8 cm.—the remainder of the uterine wall shadow being between 0.5 and 1.3 cm. (Whitehead, 1953a)—and can be seen with definition after the thirty-second week of pregnancy, when subcutaneous fat is deposited in the foetus. There is no constant relation between the dorsal and ventral aspects of the foetus and the placenta. If the placenta cannot be seen on the anterior or posterior wall or fundus, then it is either in the pelvis (placenta praevia) or implanted on the lateral uterine wall, in which case the oblique and postero-anterior views will be required. Normal implantation on the lateral wall is rare, and no such case has occurred in this series. When the placenta is calcified and normally implanted on the anterior wall its outline can be accurately demonstrated (Dawson, 1953).

(*b*) *Placenta Praevia.*—If there is placenta praevia, either the "placental shadow" cannot be seen in the upper uterine segment on the lateral and oblique radiographs of the abdomen or, more usually, the "placental shadow" disappears into the pelvis and there is an associated displacement of the foetal skull or other presenting part to be seen in the erect lateral film of the pelvis. The presenting part usually fits symmetrically into the pelvic brim when the placenta is normally implanted, and is displaced by a low-lying placenta. But displacement of the presenting part alone is inadequate for the diagnosis of placenta praevia, since this may be due to many other causes—for example, full bladder and rectum (these should have been excluded before the *x*-ray examination), pelvic tumour, disproportion, short umbilical cord. It is therefore necessary to correlate the "placental shadow" seen in the recumbent lateral films of the abdomen with the displacement of the presenting part seen in the erect film of the pelvis.

Interpretation of the radiographs tends to be difficult and less certain in the following circumstances:

Before the Thirty-second Week of Pregnancy.—In a premature foetus before the thirty-second week, the subcutaneous fat is insufficient to reveal its outline, and the foetal skull is small in relation to the pelvic brim. Ante-partum haemorrhage is rarely serious before the thirty-second week, and in most patients it is possible to repeat the examination at the thirty-fourth or thirty-sixth week, when a more definite opinion can be given.

Abnormal Presentations.—These are a common complication of ante-partum haemorrhage and placenta praevia in particular. In this series there were 4 abnormal presentations in 20 cases of placenta praevia, and 3 abnormal lies in 24 cases of ante-partum haemorrhage with a normally implanted placenta. If possible, the examination should be repeated after version.

Hydramnios and Multiple Pregnancy,—These are infrequent complications of ante-partum haemorrhage, and the problem has not occurred in this series.

After viewing the radiographs one of the following reports is submitted: (1) "The placenta is situated in the upper uterine segment on the anterior or posterior wall or fundus." (2) "There is a placenta praevia situated on the anterior or posterior wall." (3) "There are radiological signs that the placenta is implanted low on the uterine wall, and it may be a placenta praevia."

If there is doubt regarding a normal implantation of the placenta the case must be reported as one of potential placenta praevia and the patient must remain in hospital.

Obstetric Management

On admission, prior to which no vaginal examination should be made, the blood group of the patient is ascertained, and a haemoglobin estimation made, followed by transfusion if necessary. Whether or not each case requires radiological investigation will depend on the clinical findings, and it is thought to be unnecessary in cases of obvious accidental haemorrhage. Where the bleeding may be due to a possible placenta praevia an *x*-ray examination is carried out.

Where possible, it has been the practice to avoid vaginal examination until after the thirty-eighth week of pregnancy. Such examination should be conducted in the operating theatre under anaesthesia, arrangements being made for immediate section should this be required.

Prior to the introduction of location of the placenta by radiography, patients admitted some weeks before term with a possible diagnosis of placenta praevia had to remain in hospital under supervision until the diagnosis could be confirmed or disproved by vaginal examination. In this hospital, after a three-year trial period, a patient whose placenta has been radiologically confirmed to be normally implanted is discharged from hospital one week after the cessation of haemorrhage, provided her general condition is satisfactory. A gentle speculum examination is made in the theatre rather than the ward one week after haemorrhage has stopped, to exclude bleeding from an extraplacental site—for example, a polyp or carcinoma of the cervix. Cases in which there is any doubt regarding the placental site are retained in hospital.

Results

The cases of ante-partum haemorrhage admitted during 1951–3 are analysed in Table I.

TABLE I.—*Cases of Ante-partum Haemorrhage Admitted* 1951–3

Placenta praevia	33
Accidental haemorrhage	31
Local external causes	4
Undiagnosed	43
	111

TABLE II.—*X-ray Examinations for Location of Placenta in Ante-partum Haemorrhage*

Diagnosis		Confirmation	
Placenta praevia	20*	Caesarean section	14
		Vaginal examination	5
		Necropsy	1
Normal implantation	24	Normal deliveries	24
Final report doubtful	3	Placenta praevia	3
	47		

* Including 4 cases diagnosed before haemorrhage occurred.

All radiological diagnoses of placenta praevia were confirmed (Table II), and some of these cases were submitted to caesarean section without a preliminary vaginal examination in order to shorten the time that the mother and foetus were under the anaesthetic before delivery. There was direct confirmation in only one of the cases diagnosed as a normal implantation in which the placenta was manually removed; but in no case was there any indirect evidence to the contrary. Normal implantation of the placenta has been reported in numerous other cases, not included in this series, without contradiction. The three doubtful reports were made in cases in which the foetal head appeared to be engaged in the pelvic brim; but in each case a vaginal examination discovered a Degree I or II placenta praevia, for which vaginal delivery was allowed, with successful results.

From Table III it is obvious that half the cases, and nearly all those not submitted to *x*-ray examination, were admitted in labour, with vaginal delivery during the next 36 hours.

TABLE III.—*Cases of Ante-partum Haemorrhage not X-rayed*

Vaginal delivery shortly after admission (placenta praevia, 7; accidental, 12; undiagnosed, 34)	53
Emergency caesarean section (placenta praevia)	3
Severe accidental haemorrhage	4
Local external causes	4
	64

Conclusions

The results obtained in locating the placental site by plain radiography prove that the technique is reliable enough to justify its adoption as a routine procedure in general hospitals, and this assertion is supported by the findings of other investigators (Reid, 1953; Whitehead, 1953b).

The use of contrast media is regarded as unjustifiable in the investigation of ante-partum haemorrhage at this hospital, and to have no advantages over plain radiography combined with clinical examinations. Amniography has too many risks; cystography is unreliable, especially if the placenta is posterior; aortography (Hartnett, 1948) and retrograde femoral arteriography (Sutton, 1952) are too drastic for routine purposes.

Plain radiography cannot displace vaginal examinations entirely, and the two examinations are complementary, since by the former one is unable to assess the degree of placenta praevia. In selected cases the radiological diagnosis of a placenta praevia has justified caesarean section without preliminary vaginal examination.

Patients who have no obstetric abnormality and are definitely reported to have a normal placenta may be discharged for home confinement, thus saving hospital beds.

The fact that radiography will confirm a clinical suggestion of placenta praevia should prove a further stimulus to obstetricians to discover this abnormality before bleeding occurs.

Summary

The technique of placental location by plain radiography at the Royal Hampshire County Hospital during 1951–3 is described and the results are analysed.

The method is considered to be reliable, and it is concluded that: (*a*) all cases of ante-partum haemorrhage, excluding obvious accidental haemorrhage with severe toxaemia, should be *x*-rayed before vaginal examinations are performed; and (*b*) if a normally implanted placenta can be diagnosed without doubt radiologically, and there are no other complications, then the patient may be discharged.

We wish to thank Dr. C. J. Penny and Mr. Geoffrey Hammond for permission to use various cases and for encouragement in this work.

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A QUICK AND SIMPLE METHOD FOR BLOOD-SUGAR ESTIMATION

BY

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Without blood-sugar estimations the recognition and proper treatment of hyperglycaemia and hypoglycaemia may be difficult. Emergencies may arise in domiciliary practice or in hospital at a time when no routine laboratory facilities are available. A simple method of blood-sugar estimation which can be carried out in a few minutes would therefore be useful: such a method is described here.

The method presented is that originally described by Sumner (1921, 1924–5, 1925), who utilized the change in colour from yellow to red when the sugar in a deproteinized blood filtrate is heated with dinitrosalicylic acid in alkaline solution. The modifications effected are essentially that the scale is reduced to the micro level and that dinitrosalicylic acid itself is used as a protein precipitant, in which capacity it is very efficient. The excess of the acid in the filtrate is adequate for the subsequent development of colour. Finally, a set of permanent artificial colour standards has been devised.*

Experimental

Proportion of Reagents.—0.2 ml. of blood was added to 1 ml. of 1.75% dinitrosalicylic acid to yield a deproteinized filtrate, and to this filtrate an equal quantity of alkaline reagent was added.

Colorimetry.—Colour standards made directly with dinitrosalicylic acid and glucose solutions were found to fade after a few weeks even if kept in sealed tubes. This difficulty was overcome by using the Ilford filter No. 6/53, which matched the colour corresponding to a blood sugar of 70 mg./100 ml. By using additional thicknesses of this filter it was found that each extra film corresponded to an increment of 40 mg./100 ml. up to 350 mg./100 ml. Thus it was practicable to compose a set of stable artificial colour standards from the Ilford filters. As the difference in colour between any two adjacent filters was easily detected, it was possible to make an approximate evaluation for intermediate colours.

Findings

Two hundred determinations were performed on blood samples produced by the addition of measured quantities of glucose to oxalated whole blood to give blood-sugar values evenly graded in the range 80–560 mg./100 ml. The results clearly demonstrated that the developed colours were reproducible.

As the blood-sugar values increased above 360 mg./100 ml. it became progressively more difficult to detect colour differences associated with small increments of blood sugar. However, by diluting the more intensely coloured solutions with water, blood sugars in the upper range could be correctly estimated. The dilution technique was investigated by experiments using glucose solutions in the presence of the concentration of dinitrosalicylic acid found in a deproteinized blood filtrate; by this method it was found that the upper limits of usefulness could be extended to the region of 1,400 mg./100 ml.—that is, diluted four times, this colour approximately matched that colour developed from a blood sugar of 350 mg./100 ml. The lower limit of usefulness of the method was found to be about 60 mg./100 ml.

Photoelectric examinations of the colours showed that there was a rectilinear relationship between absorption of light and sugar concentration between 90 and 300 mg./100 ml. The Hilger-Spekker absorptiometer was employed, using filter No. 605. This result is in agreement with the findings of Leech and Woodford (1948) and Hall (1950). The colour is stable for at least 30 minutes at room temperature, answers obtained by immediate and delayed reading not differing by more than 5%.

A comparison of results by this dinitrosalicylic acid method using a colorimeter, and a Hagedorn and Jensen estimation performed on the same glucose solutions, is given in the Table.

Blood-sugar Estimations by the Dinitrosalicylic Acid Method Using a Colorimeter, Compared with the Hagedorn and Jensen Method

Hagedorn and Jensen	Dinitrosalicylic Acid Method with Klett Colorimeter*
90 mg.	83 mg.
135 „	144 „
243 „	236 „
305 „	288 „
395 „	383 „
500 „	444 „†
600 „	576 „†

* Colorimeter standard was the colour developed from 180 mg./100 ml. glucose solution.
† Solution diluted 1/2 for estimation.

Proposed Method

Apparatus.—(1) Test-tubes. It is essential that the tube used for colour development should be of standard bore: external diameter 0.95 cm.; internal diameter 0.8 cm. A convenient length is about 7.5 cm. The tube is graduated at intervals of 0.2 ml. to the 2 ml. mark. (2) Pipettes, 0.2 ml. and 1 ml. (3) Filter funnel, 2.5 cm. diameter. (4) Filter paper: Whatman No. 1, 4.25 cm. diameter. (5) Pasteur pipette. (6) A set of artificial colour standards calibrated to give values corresponding to those given by the Folin–Wu blood-sugar method.

Reagents.—(1) 1.75% 3:5-dinitrosalicylic acid solution in water. If the acid crystallizes out on standing, the crystals will dissolve on gently warming the solution. (2) Alkaline reagent: 13.8 g. phenol and 13.8 g. sodium bisulphite ($NaHSO_3$) are dissolved in 350 ml. 10% sodium hydroxide and added to a solution of 510 g. Rochelle salt in 880 ml. of water. This alkaline reagent is stable for about nine months.

Procedure.—0.2 ml. of capillary blood is pipetted into 1 ml. of dinitrosalicylic acid solution contained in a test-tube. If a 1-ml. pipette is not available one of the graduated test-tubes can be used for measuring the dinitrosalicylic acid solution, but some accuracy will thus be sacrificed. When the blood is pipetted it should be allowed to flow freely into the acid and only the last drop expelled by blowing. (Acid is not sucked up into the pipette, as this leads to difficulty in cleaning the pipette later. Use of the same technique in calibration of the colour standards has accounted for the blood left in the pipette.) After mixing, enough time is allowed for the colour to become brown (about 30 seconds); then the contents are filtered into a graduated tube. When a suitable volume (to the 0.4 ml. mark) of filtrate has collected, an equal volume of alkaline reagent is added by means of a dropper. The contents are mixed, and are heated in a boiling-water bath for three minutes. The tube is cooled and the colour of the contents is matched against the standards. The comparison is best made with the test and standards about four inches (10 cm.) from a 60-watt bulb. The capacity of the tube is such that its graduated section also allows for any reasonable dilution with water necessary to bring the very high

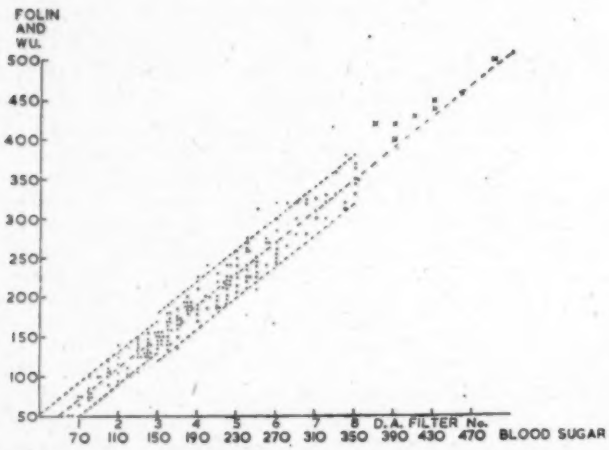
*Reagents and artificial colour standards can be obtained from British Drug Houses. The standard-bore tubes, suitably calibrated, can be obtained from Scientific Supplies Ltd.

blood-sugar colours within the range of the standards, in which case a factor would have to be applied to the answer.

Results

Blood sugars of 204 diabetics attending the Out-patients' Department of King's College Hospital were estimated by the Folin–Wu method and by the dinitrosalicylic acid method. The two series of estimations were made in different laboratories.

The accompanying Graph compares the results of the blood-sugar determinations by the Folin–Wu method with those obtained by the present method. It can be seen that



Blood sugars by the Folin–Wu and the dinitrosalicylic acid (D.A.) methods. Middle interrupted line, 100% correlation. Outer interrupted lines drawn 20 mg. from centre line below 150 mg. level, and 30 mg. above 150 mg. level. Crosses refer to those estimations for which the colours were diluted 1/2. $y=27.2+41x$ where y = blood sugar in mg. and x = filter number. Correlation coefficient, $r=0.97$. Standard error of estimate = 17.3 mg.

most of the results by the rapid method are within 20 mg. of the answer given by the Folin–Wu method. The crosses represent those determinations for which the colours were diluted 1/2 to bring them within the range of the standards.

For blood-sugar values (determined by the Folin–Wu method) in the range 60–150 mg./100 ml., 65 out of 70 results did not have an error exceeding 20 mg.; in the range 151–350 mg./100 ml., 125 out of 134 results were within 30 mg. of the determined value. Statistical analysis of the correlation is given on the graph, and was based on the first 170 blood-sugar values below 400 mg./100 ml.

The error of the higher values above 400 mg./100 ml. was not established, as sufficient estimations in this range were not made; however, estimations with glucose solutions indicate that in the range 351–700 mg./100 ml. the error was about 60 mg., and above this range the error may be as high as 80–120 mg.

Summary and Conclusions

A rapid method is described for the estimation of blood sugar.

The method takes about ten minutes to complete and gives values in good agreement with those obtained by standard methods; little apparatus or technical skill is required.

It offers a quick and reliable way of estimating the approximate blood sugar in hyperglycaemia and of detecting the presence of hypoglycaemia. In hypoglycaemia, accurate estimations are of importance in certain circumstances, but it would involve no serious disadvantage in ordinary practice to use a method which can indicate blood sugars below normal, even though it fails to estimate them precisely. Thus the method should be of value both as a ward test and as a simple aid to the general practitioner in the management of patients with diabetes mellitus.

I am grateful to Mr. H. R. Millar for his help and encouragement. My thanks are offered to the Departments of Biochemistry of Charing Cross Hospital and King's College Hospital for advice on biochemical aspects of the problem; to the physicians of the diabetic clinic of King's College Hospital for facilities to work in the clinic; and to numerous members of the technical staff of the Department of Physiology, Charing Cross Hospital, for their assistance in the preparation of reagents. I am also grateful to Mr. K. Browne for advice on statistics.

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Medical Memoranda

Phenylbutazone and Renal Function

A number of toxic manifestations have been reported in the British and American press associated with the use of phenylbutazone. Several deaths have occurred. Symptoms have included sodium retention, gastric haemorrhage, agranulocytosis, anaemia, and purpura.

In one fatal case the pathologist found contracted kidneys (*British Medical Journal*, 1952). In the case reviewed here contracted kidneys were again found, together with a history of toxic manifestations, after only a very small dose of phenylbutazone, and it is suggested that poor renal function may prove to be an important contraindication to use of the drug.

Case Report

A woman aged 65 had had arthritis for more than 30 years. During the past seven years she had had many acute exacerbations of rheumatoid arthritis with red, hot, swollen painful joints, particularly affecting the shoulders, elbows, and hands. She had been bedridden for some years. In September, 1951, sodium aurothiomalate, 0.01, 0.02, 0.05 g., was given at weekly intervals. Then albuminuria was reported and the drug was stopped. In March, 1952, minute doses of sodium aurothiomalate were tried again, 0.001, 0.002, 0.002 g., but further albuminuria was reported and the drug was again stopped.

On February 25, 1953, a course of phenylbutazone was started, one 200-mg. tablet twice a day. At the beginning of March, after taking only 13 tablets, she developed a sore throat and the drug was immediately stopped. She refused hospital treatment or investigation but agreed to have a blood count taken at her home on March 17, and this was reported as follows: erythrocytes, 2,450,000 per c.mm.; haemoglobin, 44%; colour index, 0.9; leucocytes, 3,100 per c.mm. (polymorphonuclears 57%, eosinophils 2%, lymphocytes 36%, monocytes 5%).

Her condition remained poor. She appeared to get steadily more anaemic, and a further blood count on April 13 showed: erythrocytes, 1,570,000; haemoglobin, 26%; colour index, 0.84; leucocytes, 3,400 (polymorphonuclears 40%, lymphocytes 60%). The red cells showed marked anisocytosis and hypochromia. She became comatose on April 14, did not regain consciousness, and died on April 16.

Post-mortem Examination (April 18).—External features: Elderly woman with swelling of elbows, wrists, ankles, and knees, and some fusiform enlargement of fingers with ulnar deviation. Numerous purpuric spots up to 1 in. (2.5 cm.) in diameter on the body, but mainly on the legs. Circulatory system: completely adherent pericardium; fairly marked enlargement of heart due mainly to hypertrophy of the left ventricle; coronaries, aorta, and other vessels

normal for age of subject. Respiratory and nervous systems normal. Alimentary system normal; there was no sign of ulceration of the mouth, fauces, tongue, etc.; liver, gall-bladder, and ducts normal. Genito-urinary system: both kidneys in the last stage of chronic fibrosis and contraction. The two organs together weighed less than 3¾ oz. (135 g.). The capsules stripped with great difficulty, leaving a torn shrunken granular surface.

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Squamous Epithelioma probably Due to Tar Ointment in a Case with Psoriasis

Squamous epithelioma arising as a result of chronic irritation by coal tar or its products is well known. The so-called tar warts in tar-workers are common. O'Donovan (1920) has observed that malignant change in these warts is easily remarked by the patient. It has also been repeatedly noted that it is the cumulative effect of regular exposure to tar products that works mischief. It might therefore be expected that squamous epithelioma would not be uncommon following the prolonged use of crude coal-tar ointment. Such occurrences are fortunately exceedingly rare. Henry (1946) could find only two references to cutaneous carcinoma (both fatal) related to the use of tar ointment. Moreover, he stated that in all probability both of these patients had received medicines containing arsenic, so that tar ointment might not have been entirely to blame. In a subsequent Hunterian lecture Henry (1950) stated that he had not been able to trace a single case of psoriasis (presumably associated with epithelioma) treated by a tar ointment or bath in which the patient had not also had arsenical treatment.

Prosser White (1928) quotes a case of cancer of the abdominal wall after continuous application of tar ointment. Squamous carcinoma associated with psoriasis is also a rarity. Alexander (1921; quoted by Keil and Trosow, 1948) could trace only 18 cases in the literature. In 11 of these there was a history of arsenic ingestion. Hannay (1949) reported a case associated with arsenic administration over a period of eight years, and reviewed the literature containing at least 10 cases. About half of them gave a history of having taken arsenic for long periods. Six of the cases were basal-celled epitheliomata. Hannay quoted Wright and Friedman as stating that arsenical epitheliomata which developed in persons with psoriasis almost invariably arose independently of that disease.

We present a case of squamous epithelioma arising on a patch of psoriasis. No history of arsenic administration could be traced, and the only agent applied to the skin that might have been carcinogenic was tar ointment.

CASE REPORT

In October, 1952, a man aged 31 reported to the surgical out-patient department of Glasgow Royal Infirmary. He complained of a small lump about 2 cm. in diameter over the head of the right fibula. The lesion was raised about 3–4 mm. above the surface of the skin. The edge was firm and rolled, and the centre showed slight ulceration without discharge. The lesion, which was superimposed on a patch of psoriasis, resembled the so-called button epithelioma. There was a diffuse discoid psoriasis and a marked tar acne with one or two of the lesions known as "tar mollusca."

The psoriasis began on the backs of the hands in 1943 whilst he was serving in Tunisia. It was treated successfully with some form of violet ointment. Nine months later, when he was in Italy, it relapsed. It had recurred since at intervals of about one year. He denies having had any internal medicines for the condition at any time. When he reported in October, 1952, he had been gettting local treatment with:

Salicylic acid	6%
Oleated mercury	20%
Coal tar	20%
Emulsifying base	q.s.

After 14 days on this ointment he developed "pimples with crusts" over the treated areas—the thighs and legs. Although these lesions were annoying and somewhat itchy, he did not seek advice, but continued to use the ointment for three months.

The epitheliomatous lesion was excised and the diagnosis of squamous carcinoma confirmed histologically. The scar was treated with contact *x*-ray therapy after it had healed.

COMMENT

There seems to be no doubt that the epithelioma in this case resulted from the overzealous use of an ointment containing coal tar. The latter substance is one of the standbys of the dermatologist. It is used in large quantities, often for long periods over extensive areas, for such chronic skin conditions as eczema, Besnier's prurigo, neurodermatitis, psoriasis, etc. Tar acne occurs in an appreciable proportion of cases, and is an indication for its immediate withdrawal. The absence of reports of epithelioma from the use of tar ointments suggests that such an event must only rarely occur. Cases of tar epithelioma of industrial origin are almost invariably accompanied by a pronounced tar acne which has been present for years. Moreover, the patient has usually remained at work with his tar acne, which has continued to be irritated by the offending tar product. It seems that the continued insult to the skin, after the initial appearance of signs of tar irritation, is the essential factor in the production of malignant change. Such persistence of irritation by the carcinogenic agent does not occur in patients treated with tar ointment, because the signs of irritation are recognized early and the application is withheld.

In the case presented above, a typical fairly severe tar acne was present after two weeks' application of tar ointment. The patient, ignorant of the risk, continued to use the ointment for three months, after which period the epithelioma developed. In contrast to the superficial splashing of the skin with tar products in industrial tar acne, in this case the offending tar product was actively rubbed into the skin. The ointment used contained 20% crude coal tar in emulsifying base. This is approximately equivalent to 40% crude coal tar in soft paraffin or lanolin. There is much more penetration of the skin when emulsifying base is used as the ointment vehicle. Even so, the period of irritation by tar was relatively very short. In O'Donovan's series of 16 cases of industrial tar epithelioma, the minimum period of working with tar prior to the onset of carcinoma was 10 years.

It is of interest to note that the epithelioma in the present case arose on a patch of psoriasis. Hannay (1949) has quoted Wright and Friedman and also Ormsby and Montgomery as stating that this is most unusual in cases in which the two conditions are concomitant. The application of tar ointment, even for a short period, may be fraught with danger if it is accompanied by tar acne.

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Reviews

EAR, NOSE, AND THROAT

Modern Trends in Diseases of the Ear, Nose, and Throat. Edited by Maxwell Ellis, M.D., M.S., F.R.C.S. Modern Trends Series, under the general editorship of the Rt. Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P. (Pp. 471; 140 figures. 65s.) London: Butterworth and Co. Ltd. 1954.

This book consists of a collection of admirable essays by experts. The first thirteen chapters are devoted to the ear; then come five on the nose and nasopharynx, followed by six on the larynx and one each on pharyngeal diverticulum, cancer of the pharynx, the oesophagus, and speech therapy for children with cleft palate; the last chapter deals with radiology.

The first chapter, on the functions of the labyrinth, is by Professor W. J. McNally and Dr. E. A. Stuart, of Montreal, who make a most helpful contribution to a difficult subject. The chapter on laryngoscopy and bronchoscopy and another on the oesophagus come from Professor P. H. Holinger, of Chicago. In the first of these he reviews the varieties of endoscopic tubes and their uses for diagnosis and treatment; the second contains a comprehensive account of diseases of the oesophagus. Professor LeRoy Schall, from Harvard Medical School, contributes a stimulating essay on the patient after laryngectomy. Dr. Eric Samuel, of Pretoria, shows himself extremely skilful in the radiological demonstration of details of the skull, his text being accompanied by admirable illustrations.

Terence Cawthorne deals with aural vertigo: as he says, though there are many causes of giddiness the ear is responsible for the great majority. The causes of Ménière's disease are fully discussed and the treatment given in detail. In an excellent and balanced account of the surgery of non-suppurative deafness Simson Hall points out that, while for the healed radical mastoid operation and congenital deafness due to malformation surgery is experimental, it is to-day the standard treatment for otosclerosis. Appropriately the following chapter, by Scott Stevenson, is on the non-surgical treatment of deafness. He admits that fenestration gives the only hope of improving hearing in otosclerosis, but defends the hearing-aid and stresses the importance of encouraging the deaf to learn lip-reading. The same author writes a sound article on otitis externa.

The chapter on the chemotherapy of acute aural infections comes from Dr. Friedmann, who gives an instructive table to show the virtues and vices of the commonly used antibiotics. In Chapter 10, on acute otitis media, A. R. Dingley warns against over-prescribing, and points out that surgery still has its use for releasing pus. There follows an interesting essay by A. Tumarkin on chronic otorrhoea, in which he sets forth his views on blocked tube in children and on the pathology of cholesteatoma; he describes his per-meatal operation, illustrated by pictures and excellent stereoscopic photographs. The editor writes on intracranial complications of aural infections and also on laryngeal paralysis. The causes of different types of meningitis are fully explained, and some admirable angiograms are included as a help to the diagnosis of cerebral abscess. In the second contribution he gives an account of the varieties of laryngeal paralysis and discusses the various operations for restoring an adequate airway in cases of bilateral abductor paralysis.

The chapter on facial paralysis is in the expert hands of Miss J. Collier, who recommends the use of a binocular operating microscope for operations on the facial nerve, stretching of the facial muscles being prevented by splints fixed to dental plates. She also contributes a chapter on nasal catarrh. In the following article Stirk Adams discusses upper respiratory tract infections in children. Naturally there is considerable overlap with the previous chapter. There next come two chapters by G. H. Howells on orbital and intracranial complications and osteomyelitis as the result of sinus infections. C. P. Wilson writes on tumours of the nasopharynx, which are rare in this country, and all of which, with the exception of fibroma, are malignant. Their pathology is discussed and a full account of the symptoms given, followed by a clearly illustrated description of the operation devised by the author to expose the nasopharynx. The chapter on tuberculosis of the upper air passages is by Professor Ormerod, who also writes on the treatment of cancer of the larynx.

Professor Kilner, in his chapter on stenosis of the larynx, considers that unless bougies can be passed without causing bleeding it is better to open the larynx and apply a skin graft. The operation is described, together with the technique of inserting a skin graft and the "form" to hold it in place. In an article on pharyngeal diverticulum J. H. Otty, after mentioning the anatomy and symptoms, describes the one-stage operation through the neck for relieving the condition. Cancer of the pharynx is dealt with by R. D. Owen. In this chapter the types and positions of growths and indications for excision are discussed, followed by detailed instructions for operation with illustrations of the various stages.

The authors of three chapters are non-medical. A physicist, Dr. Littler, writes on hearing tests and hearing-aids; as might be expected, he gives a critical review of electronic audiometry and its limitations. Professor Ewing's authoritative article on children with defective hearing is perhaps the most interesting in the book and certainly justifies the title of "Modern Trends." His chapter brings up to date the problem of the education of deaf children. Margaret Eldridge, speech therapist at St. Vincent's Hospital, Melbourne, gives an instructive account of speech therapy for children with cleft palate. She has found that many of these children also suffer from some degree of deafness, and considers that in their treatment the departments of otology, psychology, orthodontics, and education must collaborate.

This is a book for the specialist. The printing is clear and there is a good index, though some of the entries are a little puzzling at first sight—for example, "Tumours, histological nature of, larynx, cancer of, in."

W. M. MOLLISON.

HEALTH IN INDUSTRY

Mental Health and Human Relations in Industry. Edited by T. M. Ling, M.A., D.M., M.R.C.P. Foreword by the Rt. Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P. (Pp. 265 +xix; illustrated. 21s.) London: H. K. Lewis and Co., Ltd. 1954.

In both world wars emphasis on industrial productivity attracted attention to medical problems concerned with fatigue, morale, and the psychological conditions of work. World War I led to the establishment of the Industrial Health Research Board and to a long series of investigations promoted by the Medical Research Council. About 15 years ago Elton Mayo and his co-workers in the U.S.A. began to discuss the role of human relations in health and productivity, and since then increasing attention has been paid to this aspect of the subject. Human relations are not easy to study, and in industry, where health is not the primary aim, it is even less easy for the doctor to find a role in which he can directly influence human relations in order to promote health; but the Tavistock Institute in their well-known research in a single factory did gain the co-operation of management and workers in a participant study which aimed at resolving tensions in a therapeutic fashion.

It is with this background of information and with the experience of treating some thousands of workers at Roffey Park that this book is written. Nevertheless it does not reach the standards of presentation which we expect of a treatise or a textbook, because the subject has a very long way to go before enough facts are amassed to make this possible. Where facts are lacking the discourse proceeds by interposing hunches and value judgments, which is not too serious a defect if in the future there is to be an earnest endeavour to test hypothesis by experiment and survey; but in this field, where experiment is so difficult, there will always be a great temptation to get on with the good work instead.

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One's confidence in the quality of the work is shaken by the presence of fairly numerous slips and errors in the text and references. For instance, there are several such errors in the references to Chapter I which will baffle those who are stimulated by the book to read further.

T. F. RODGER.

POISON SMOG

Air Pollution and Community Health. By Clarence A. Mills, M.D., Ph.D. (Pp. 180. $2.75.) Boston: Christopher Publishing House. 1954.

The deliberate coining of new words is an enterprise to be approached with caution, because, like the intentional spreading of myxomatosis in rabbits, the results cannot be foreseen or controlled. The invention of the ugly hybrid "smog" and the more recent introduction of the word "murk" as a unit of measurement of dirt in the air appear to be fully justified in that these novel and unpleasing terms may help to stimulate more interest in the offensiveness of smoke pollution. The Beaver Committee has not hesitated to refer to smog, and the author of this book fairly plugs the word as a good propagandist should. But maybe the limit has been reached when he refers to fine dust as "submicronic."

The somewhat uninviting title of this book does not do full justice to its content. There is the usual presentation of fact and opinion about air pollution and its evil effects, but there is also the flash and the clash of bright steel as Dr. Mills fights the anti-smoke battle, and a pungency like that of the sulphur dioxide he so rightly abhors.

There is an entertaining chapter on "Politics and Pressures" and a lurid description of a smog disaster in an American city. There is also an amusing account of the activities of Abe, a restaurant proprietor and farmer who engaged in a hard-fought campaign for "Clean Air and Green Grass." We are told that when Abe proposed to bring new livestock into a polluted inhabited area in an endeavour to study the effect of smog on their health he was informed that if he did "he would be prosecuted for such an act as one of wanton cruelty to animals"! Abe's crops were ruined several times by sulphur fumes, and he reacted vigorously, recalling a somewhat similar case in Lancashire in 1925 which reached the Law Courts in 1930.

This book makes good, easy, and profitable reading, and incidentally contains more than enough material for a Sinclair Lewis type of novel.

C. METCALFE BROWN.

STRESS

Third Annual Report on Stress. By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), and Alexander Horava, M.D. (Lausanne). (Pp. 637; illustrated. 80s.) Montreal: Acta Inc., Medical Publishers. 1953.

This volume represents the third of a series of annual supplements to Professor Selye's *Stress (The Physiology and Pathology of Exposure to Stress).* In broad outline the book is similar to the second report of the series (for review see *British Medical Journal*, 1953, **2**, 477). After an introductory section, which deals with the views of the Montreal school on various aspects of the general adaptation syndrome and the so-called diseases of adaptation, the book is divided into two parts. Part I deals with the general physiology and pathology of stress, and Part II with the special physiology and pathology of stress according to the systems of the body. The presentation of this material is as a classified index relative to the pertinent literature. This comprehensive and up-to-date list of 5,700 papers probably forms as nearly complete a reference to the recent publications on the subject as is possible. With a little practice the reader is enabled to obtain quick reference to the papers that have appeared on any particular aspect of the subject. No indication is given of the value of the publications listed, so that in some cases time may be wasted obtaining an obscure journal that eventually does not appear to merit the effort taken.

A new addition to this volume is the inclusion of a series of special articles by authorities in their own fields: "The Effects of Bilateral Total Adrenalectomy in Diabetics with Advanced Vascular Disease," by J. T. Wortham and J. W. Headstream; "Neurophysiological Aspects of the Control of A.C.T.H. Secretion," by R. W. Porter; and "Hypertension," by D. M. Green. These are original reviews and have not been subjected to editorial alterations. The final section of the book is concerned with a sketch for a Unified Theory of Medicine. The twenty pages devoted to this topic are highly philosophical and might perhaps have been better presented as a separate publication.

This third annual report is, as usual, very well produced; it is expensive, but forms a useful addition to medical libraries for reference purposes.

G. W. HARRIS.

ARTIFICIAL HIBERNATION

Pratique de L'Hibernothérapie en Chirurgie et en Médecine. By H. Laborit and P. Huguenard, with the collaboration of twenty-one others. Preface by C. Jaulmes. (Pp. 256+vii; 13 figures. 1,400 fr.) Paris: Masson et Cie. 1954.

Artificial hibernation is a method, or rather state, of anaesthesia about the value and nature of which there is still considerable difference of opinion, even in France, its home. Those who practise it in Great Britain are in the minority. The now considerable literature about this technique and about chlorpromazine, the principal drug used in it, is summarized—not very concisely perhaps—in this book. Drs. Laborit and Huguenard, who have throughout been the main proponents, if not the inventors, of the method, have extracted everything they could from their own experience, and have added a great deal of other, sometimes only distantly related, material. Unfortunately the important pharmacological work of Burn on chlorpromazine was published too late to be included, and many of the statements in the book must be reconsidered in the light of Burn's work. The anaesthetist on going through the book is likely to have the feeling, however, that chlorpromazine and artificial hibernation have had, to borrow a Hollywood expression, a great "build-up," and that perhaps too many positive statements about the method have grown out of too little general anaesthetic experience and comparative objective assessment. Very extensive bibliographies have been included. The book is the best available account of this very controversial subject.

W. W. MUSHIN.

CHILD PSYCHIATRY

The Child, His Parents and the Physician. By Hale F. Shirley, M.D. (Pp. 159; illustrated. 27s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1954.

A new book on child psychiatry may be looked on askance by the average paediatrician, but this one is full of common sense and is a most acceptable addition to any paediatric library. It would also be excellent for parents, being couched in comprehensible terms throughout. There are some amusing and instructive drawings, and to say that the book is published by Charles C. Thomas of Springfield is a sufficient guarantee of the excellence of the format and printing.

The author holds the unusual post of professor of paediatrics and psychiatry, and this perhaps explains his approach to the subject. The book is a monograph in the American Lecture series, and every one of its 152 text pages is well worth reading. There are two pages of suggestions for further reading at the end of the book, though many readers will be satisfied with the contents of the book itself. The subject is discussed under the emotional needs and development of the child, the developmental tasks of infancy and childhood, socialization of the emotions, adaptive techniques, and emotional imbalance. The last two chapters deal with interviewing of patients and counselling of parents.

W. GAISFORD.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY NOVEMBER 6 1954

ROYAL HONORARY MEMBER

This week has witnessed two notable events in the history of the British Medical Association. On Tuesday afternoon the Archbishop of Canterbury dedicated the impressive war memorial designed by Mr. James Woodford in collaboration with Mr. S. Rowland Pierce, and in the evening the Duke of Edinburgh was admitted an Honorary Member of the Association during dinner with the Council in the hall where King George V, nearly thirty years ago, opened B.M.A. House in July, 1925. The links between the Royal House and the medical profession are from the nature of things closer, we like to think, than those with any other section of the community. And the link forged between the Royal Family and the B.M.A. over fifty years ago, when in 1901 King Edward VII became our patron, is one deeply and loyally treasured. Since then the reigning monarch has graciously accepted the patronage of the Association, and this week the link with the Throne has been most happily strengthened by the admittance to honorary membership of the Queen's husband, the Duke of Edinburgh. The Association greets him in his capacity not only as the consort of its patron but as a man who has a lively and discerning interest in the application of science to human welfare, and in any measure—such as the National Playing Fields Association—which will promote the health of the young. The Duke of Edinburgh honours the Association by accepting its Honorary Membership, and the Association takes a keenly loyal delight in bestowing this honour upon him.

IN MEMORIAM

The Archbishop of Canterbury on Tuesday dedicated the fountain and statues erected in the Court of Honour of B.M.A. House as a memorial to the medical men and women of the British Empire and Commonwealth of Nations who gave their lives to their country in the war of 1939–45. That nearly a thousand of our colleagues died in the second world war reminds us that though the doctor is a non-combatant he is yet privileged to share some of the hazards of war with the fighting men he cares for in health, disease, and injury. However evil war may be, it is rarely without benefit to Medicine. Ambroise Paré advanced surgery through his experience on the battlefield; Florence Nightingale came back from the Crimea with a zeal to reform nursing; the two world wars of this century have vastly enlarged the frontiers of medical knowledge and skill. Out of the sacrifice and suffering symbolized in the statue of Machaon (see p. 1099) come treatment and prevention, and finally, as expressed in the fourth of Mr. Woodford's figures, aspiration towards a fuller life: in the hope and fulfilment of this last lies the justification of the sacrifice.

TREATMENT OF ADDISON'S DISEASE

The treatment of Addison's disease has become increasingly specific since 1930, when the first attempts at rational hormonal replacement therapy were made with the adrenocortical extract of Swingle and Pfiffner.[1] The administration of adrenocortical extracts is now almost wholly confined to the treatment of patients in crisis, when they are given with cortisone, deoxycorticosterone, glucose, and sodium chloride. In 1932 Loeb reported that patients with the disease benefited from receiving sodium chloride by mouth,[2] and for the next six years treatment was by a combination of the hormonal extract with salt. In 1938 Simpson[3] published the first report of a clinical trial of deoxycorticosterone.

For the last sixteen years deoxycorticosterone acetate (D.O.C.A.) has been the mainstay of treatment both for maintenance and in adrenal crisis. When the diagnosis of Addison's disease has first been made patients are stabilized with daily injections of D.O.C.A. The greatest single help in assessing the effect of treatment is the daily weight chart, the aim being to effect a gain in weight of not more than 1 lb. (0.45 kg.) a day.[4] After a prolonged period on daily injections,[5] which is necessary to find out the optimum dose to maintain the patient in reasonable health, pellets of D.O.C.A. may be implanted subcutaneously. The dosage of the implants can be calculated from the amount of the hormone needed for the daily injection,[5] although not all physicians think that a precise calculation is necessary.[6] Nevertheless without such calculation there are serious dangers of overdosage, especially after a patient has been under implant treatment for any length of time, and Greene notes that it is often necessary to reduce the implanted dose in such people.[7] The results of overdosage are hypertension progressing to cardiac failure, and biochemical disorders, culminating in extreme cases in muscular paralysis from potassium depletion.[8] More recently Kirkeby[9] described seven cases of Addison's disease in which moderately severe pains in the

joints were initiated or aggravated by treatment with D.O.C.A. There are also reports of hypertrophy of breast tissue in men occurring during treatment with this hormone[7 10] and with adrenocortical extracts.[11] As an alternative to implantation it has been found that injections of deoxycorticosterone trimethyl acetate (D.C.T.M.A.) in micro-crystalline suspension remain effective for four to eight weeks.[12] Spence drew attention to the necessity of continuing the daily maintenance dose of D.O.C.A. for two days after the first injection of D.C.T.M.A., because the absorption of the latter may be delayed.[13]

Although treatment with one of the deoxycorticosterone esters corrects the biochemical abnormalities and the hypotension of patients with Addison's disease, it has no effect on the hypoglycaemia to which these patients are prone, and which Simpson regards as one of the commonest causes of death in patients treated with deoxycorticosterone.[14] In the last two years it has been the custom to treat patients with deoxycorticosterone supplemented with small doses of cortisone by mouth.[6 10] Patients so treated show a marked increase in energy, appetite, and general well-being,[6 10] and the tendency to hypoglycaemia is lessened. In most there is a decrease in the characteristic pigmentation.[6 15]

The amount of cortisone available in Britain has precluded its use as the sole replacement hormone in all but a few cases,[5] and Thorn *et al.*[15] have reported on a larger series in America. In Britain Simpson[5] concluded from his experience in four cases that cortisone treatment was the method of choice, supplemented where necessary by additional salt and D.O.C.A. by implantation. The advantages of treatment with cortisone are that it is effective when taken orally, which D.O.C.A. is not; that it produces a great increase in the patient's appetite, energy, and vitality,[4 5 10 15] and that it overcomes the tendency to hypoglycaemia. Its disadvantages are that it is known to promote the spread of active tuberculosis, and therefore it is contraindicated in cases of Addison's disease complicated by that infection. Nevertheless, the dosage used in maintenance is within the physiological range, and Simpson does not think that the dangers of tuberculous dissemination are very great.[5] Other disadvantages are that patients treated with it still remain prone to postural hypotension; the disorders of electrolyte balance are not always wholly corrected; and there are reports of the development of psychotic symptoms in certain cases.[15 16]

While at present combined treatment with deoxycorticosterone and cortisone is the method of choice, treatment in future is likely to be with aldosterone. The isolation and characterization of this steroid by Simpson *et al.*[17] have been followed by small-scale clinical trials in Switzerland[18] and Britain.[19] The Swiss workers gave the hormone by injection, the British by mouth. The responses they elicited were substantially the same. Aldosterone restores and maintains electrolyte balance by causing sodium retention and potassium excretion. It causes the glucose tolerance test to become normal or nearly so, and in one investigation tended to increase the excretion of nitrogen.[19] It has no effect on the response to water loading. Both groups found that the pigmentation was lessened. Both concluded that it was about thirty times as potent as intramuscular injections of deoxycorticosterone. So far the amounts of the hormone isolated are so small (22 mg. from 500 kg. beef adrenal) that supplies are extremely limited even for the small dosage required. There seems little doubt that, when more becomes available, aldosterone alone, combining the advantages of both deoxycorticosterone and cortisone, and effective even in small dosage by mouth, will overcome the hormone deficiency of patients with Addison's disease.

[1] *Science*, 1930, **71**, 321.
[2] Ibid., 1932, **76**, 420.
[3] *Lancet*, 1938, **2**, 557.
[4] Smart, G. A., *Postgrad. med. J.*, 1953, **29**, 200.
[5] Simpson, S. L., *Proc. roy. Soc. Med.*, 1953, **46**, 566.
[6] de Mowbray, R. R., ibid., 1953, **46**, 577.
[7] *The Practice of Endocrinology*, 1951, 2nd ed., Eyre & Spottiswoode, London.
[8] Thorn, G. W., *et al.*, *Ann. intern. Med.*, 1942. **16**, 1053.
[9] *Acta med. scand.*, 1954, **149**, 43.
[10] Fourman, P., and Horler, A. R., *Lancet*, 1954, **1**, 334.
[11] Edwards, R. A., *et al.*, *J. Amer. med. Ass.*, 1938, **111**, 412.
[12] Thorn, G. W., *et al.*, *J. clin. Endocr.*, 1953, **13**, 957.
[13] *Proc. roy. Soc. Med.*, 1953, **46**, 575.
[14] *British Medical Journal*, 1953, **1**, 1110.
[15] Thorne, G. W., *et al.*, *Amer. J. Med.*, 1951, **10**, 595.
[16] Cleghorn, R. A., and Pattee, C. J., *J. clin. Endocr.*, 1954, **14**, 344.
[17] *Experientia (Basel)*, 1954, **10**, 132.
[18] Mach, R. S., *Schweiz. med. Wschr.*, 1954, **15**, 407.
[19] Kekwick, A., and Pawan, G. L. S., *Lancet*, 1954, **2**, 162.

GAMMA GLOBULIN AND MEASLES

Gamma globulin given to a child contact of measles at the correct time and in the correct dose will usually modify or prevent the disease. The protective substances are derived from human serum, and a dose of 9 ml. of gamma globulin is obtained from 120 ml. of serum, roughly the yield of one pint (0.6 litre) of blood. Economy in its use is obviously essential, and the first problem is to decide which children should be protected. Since the severe complications of measles are commonest under 3 years old, preference should undoubtedly be given to children below this age. The report by Drs. J. C. McDonald and W. C. Cockburn at p. 1076 of the *Journal* this week shows that, so far as home contacts are concerned, gamma globulin is in fact given most to this group. With babies under 6 months old the family doctor has to consider the problem that the attack rate in contacts of this age is only about 10%, and the authors advise that gamma globulin should be given to this group only when the mother has not had measles—a fact often difficult to be sure about. On the other hand, if a baby under 6 months does develop measles,

the attack is likely to be severe. At the risk of some waste, perhaps the safest policy for all contacts under 3 years is to give gamma globulin when the health of the child is in any way below normal. For older children, it should not be used unless the child is already suffering from another illness. In ward outbreaks the object is to render the ward free of infection as quickly as possible, and few fever hospital clinicians would agree with McDonald and Cockburn's suggestion that it might be sufficient to give protection only to children in beds adjacent to the case: measles and other cross-infections have a habit of occurring in the opposite corner of the ward.

In home contacts modification is better practice than prevention, but it is difficult to forecast what the effect of any injection will be. The authors suggest 3 ml. as a modifying dose. This is a useful working dosage, though in the younger children prevention rather than modification will often result. As regards the best time to give it, McDonald and Cockburn found that in babies aged between 6 months and 1 year delay seemed to have little effect, but in babies over 1 year the effect became more marked. In practice the doctor usually sees the case on the first or second day of the rash, so that contacts have already been exposed for four or five days and there is no time to lose. When contacts are seen earlier, it is probably wise to withhold gamma globulin until the third or fourth day if modification is desired.

Adult serum was found to be much less effective than gamma globulin. Moreover, 9 ml. of concentrated adult serum and 9 ml. of gamma globulin corresponded respectively to 45 ml. and 120 ml. of normal adult serum, so that to give comparable doses the size of the injection of adult serum would be unmanageable. Irradiation of adult serum has not removed all risk of serum hepatitis. For these two reasons pooled adult serum should no longer be used for the prophylaxis of measles. Convalescent measles serum from a single patient, however, is a reasonably safe and reliable prophylactic, but it is rarely available except for ward use in a fever hospital.

PLASTIC DRESSINGS

In its healthy state intact skin is constantly contaminated by a wide variety of pathogenic organisms. It has, however, the ability to cleanse itself by the natural process of drying and the bactericidal properties of its own unsaturated fatty acids. When the skin is broken the wound exudate neutralizes the fatty acids and may also keep the area moist, and so the first two natural barriers against the growth of skin contaminants are broken down. The wound then depends upon the vital quality of the damaged tissues to bring quickly to its aid enough leucocytes and antitoxins to combat the contaminants. Further, wound contamination is seldom caused by pathogens actually on the wounding instrument: rather the wounding instrument carries in pathogens already present on the skin. For example, the rose thorn in the sun is not at all likely to be contaminated by tetanus bacilli, and so when a gardener pricks his finger the probabilities are that the thorn carries in organisms already present on his "muck"-soiled hands —or, hours or perhaps days later, the wound being still open and unprotected, the organisms enter as added contaminants. Colebrook's[1] dictum still holds: "The longer a wound remains open the more certain it is to become infected." To which may be added a further truth that contaminating organisms should not be considered as individual species, each producing an independent syndrome of infection, but as mutually contributing to the general infection of the wound, one organism sometimes enhancing the other's growth.

Two primary functions of any wound dressing are to protect the wound from further contamination and not to interfere in any way with the vital recuperative properties of the damaged tissues. There has recently been renewed interest in the possibilities of plastic dressings, the best of which have certain admirable properties. They are non-irritant, have a fair water-vapour permeability, yet are an effective barrier against micro-organisms.[2] Not only have suitable adhesives been found to seal such dressings so that they remain in place for the time required for healing, but there are indications that to this essential adhesive quality there may soon be added an elasticity or extensibility of the dressing itself. This is a difficult demand to make of any dressing, yet, particularly in the common finger and hand injuries, the ideal cover dressing should mould itself to the contour of the skin to be covered, act as a splint to the wounded skin, and yet allow a range of useful movement. Various plastic sprays and paints, as opposed to plastic films, are in an earlier stage of development. Many now on the market are known to be wound irritants, some may well be toxic, and all are inflammable in some degree. But they have definite possibilities,[3 4] particularly as quick and easy wound cover for trivial facial wounds in children.

The wounds most suitably covered by plastic dressings should be dry. If wound exudate is excessive the degree of water-vapour permeability of plastic material does not prevent sogginess, which delays healing and may lead to infection. The application of such dressings is therefore restricted to dry surgical wounds and to minor, but very common, traumatic wounds. Many severe wounds, because of their excessive exudate or their depth, should have an absorbent dressing; some require the support of pressure and others some form of splint. These requirements are best met by the conventional gauze, cotton-wool, and bandages, with perhaps the support of a plaster-of-Paris shell.

Plastic dressings have many real and some potential advantages. The expense of covering most wounds with gauze, cotton-wool, and bandages must be very great; and the tendency for such dressings to wander off the wound is notorious, and their proper application and reapplication time-consuming. Many medical men, doubting the protective value of cover dressings, have either ceased to use them or left the matter to the discretion of nurses. Such an attitude is potentially

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[1] *A New Approach to the Treatment of Burns and Scalds*, 1950, London.
[2] Bull, J. P., Squire, J. R., and Topley, E., *Lancet*, 1948, **2**, 213.
[3] Rob, C. G., and Eastcott, H. H. G., *British Medical Journal*, 1954, **2**,17.
[4] Rigler, P., and Adams, W. E., *Surgery*, 1954, **36**, 792.

dangerous, and particularly so in the very common small puncture wounds after intravenous therapy. The practice of the future may well be to pay much more attention to all sources of wound contamination and infection, and to cover all wounds immediately by an efficient dressing best suited to the needs of a particular wound. In this context plastic dressings have already made a notable contribution.

PERIODIC MEDICAL EXAMINATION

In Britain there is a sharp division of medical opinion on the question of whether or not routine yearly medical overhaul would be an advantage to the public. To the lay person it seems obviously desirable, but the layman's views on matters medical are usually ill-informed and singularly opinionated. In the United States of America, on the other hand, such regular "check-ups" have been widely accepted as highly desirable. Many in this country are familiar with the American patient who, bred on health propaganda through the medium of wireless and monthly magazines, confidently expects not only a clinical examination but also the whole gamut of biochemical and radiological investigations of which he is aware. A powerful influence to encourage this view is exerted by those of the American life insurance offices which offer a reduction of premium and free yearly overhaul to proposers for large sums if they will agree to the examinations. Baker and his co-workers,[1] in an interesting report on the results of examining 1,350 people (chiefly of "executives"), found that obesity, osteo-arthritis, hypertension, and anaemia held pride of place in the list of diseases discovered. It is remarkable that only 167 of those examined were passed as fit. Baker was careful not to include unimportant abnormalities such as flat foot in the list; but obesity was regarded seriously if the body weight was 10% or more above the ideal weight.

The fact which stands out from Baker's communication is that an experienced clinician should be able to diagnose almost all the diseases he discovered without any of the ancillary investigations. It goes without saying that a full overhaul must include examination of the rectum. No case seems yet to have been made out for routine radiography of lungs, alimentary tract, or other parts, or for the use of the electrocardiograph. Even if extensive *x*-ray, blood, and electrocardiographic investigations were made they might not reveal the presence of disease already present; or they might give rise to undue alarm by exposing some abnormality best ignored. A more general objection to periodic medical examinations is the likelihood that a "negative" overhaul will engender a false sense of security. Much can happen from one year to the next. For instance, a man whose symptoms suggested an obstructive lesion of the colon was reassured by a normal skiagram of a barium enema. He died of a perforated bowl, blocked by carcinoma, four months later. Again, a firm believer in half-yearly overhaul, with any investigations which might bear on symptoms, no matter how slight, developed abdominal discomfort two months after an examination. He delayed matters because of the previous reassurance. Three months later he was found to have an inoperable carcinoma of the transverse colon. On the other hand, one doctor lived in fear of his life for ten years because of a chance electrocardiograph finding of bundle branch block—he still lives, though no longer in fear, twenty years after the discovery.

Abrahams[2] subjects the cult of periodic medical overhaul to pungent and lucid criticism, and rightly points to the value of interrogation as a fruitful approach to discovery of disease. It is true, as he says, that such a method of investigation calls for considerable experience. Experienced physicians have declared that the longer they live the more value do they attach to anamnesis followed by a careful, but intelligently directed, physical examination. We should therefore continue to urge the public to seek advice for any symptom of illness. We should not delude them into the belief that periodic visits to the doctor will ensure good health.

[1] *Sth. med. J. (Bgham, Ala.)*, 1953, **46**, 984.
[2] *Lancet*, 1953, **2**, 670.

LUPUS VULGARIS FOLLOWING B.C.G.

The establishment of specific immunity to disease may sometimes be brought about by inoculation of killed cultures or by extracts of such material. In other cases, however, a living organism has to be used so as to set up a mild or modified infection under conditions which can be more or less controlled. This type of preventive vaccination was the kind first introduced for smallpox, and the virus used was specially attenuated by passage through cattle. By this passage the organism loses some of its virulence, but, in spite of this, generalized vaccinia occasionally follows ordinary vaccination. In particular, one form of Kaposi's varicelliform eruption or eczema vaccinatum may result when inoculation is practised on infants suffering from atopic eczema.

In recent years the bacillus of Calmette and Guérin has been used on an increasingly wide scale for the production of modified tuberculosis in the human subject with the object of setting up active immunity to the more serious natural disease. The usual result of this inoculation is the production of a primary tuberculous chancre of low-grade virulence; infection is self-limiting and gives rise to immunity as evidenced by the development of a positive Mantoux reaction. The spontaneous tuberculous chancre occasionally seen in children and more rarely in older people most often clears up completely, but it may leave a residue of lupus vulgaris, tuberculous lymphadenopathy, or, much more rarely, remote or disseminated tuberculosis. It is therefore not surprising that inoculations with B.C.G. may rarely produce a lesion which is not self-limiting but which persists in the skin with the clinical characteristics of lupus vulgaris. B.C.G. vaccination has been carried out in Denmark on a large scale in recent years, and Dr. P. V. Marcussen[1] now records from the clinical material of the Finsen Institute two cases and a possible third in which slowly progressive lupus vulgaris has

[1] *Brit. J. Derm.*, 1954, **66**, 121.

appeared on the site of inoculation; or perhaps it is more correct to say that the site of inoculation is scarred and more or less healed, and that lupus vulgaris has developed in the immediately surrounding skin. In one of these cases the axillary lymph glands were involved. No other evidence of tuberculosis was found in these patients and the Mantoux reaction was positive. Dr. Marcussen points out that this brings the total of similar cases to six so far reported, but he emphasizes that this rare complication of B.C.G. vaccination should not influence the general assessment of this type of inoculation. It does, however, suggest the need for following up patients for a few years after the inoculation in order to make sure that this complication does not develop.

IDIOPATHIC HYPERLIPAEMIA

Some milkiness of the serum due to transient hyperlipaemia after a fatty meal is well recognized by workers dealing with large numbers of blood samples. In certain conditions such as diabetes mellitus or nephrotic syndrome it may be particularly marked. In addition to this secondary hyperlipaemia there is a type in which the hyperlipaemia is obvious and persistent without apparent cause. Known as primary or idiopathic hyperlipaemia, it was first described by Bürger and Grütz,[1] and since then some twenty-seven cases have been reported. Malmros, Swahn, and Truedsson[2] have recently published details of ten further patients with this rare but interesting condition.

The clinical picture is variable. In Malmros's series all the patients were aged over 40, though a number of cases have occurred in young adults and children. He found skin xanthomata in half his cases, and, what is of greater importance, five of his ten patients had well-established coronary artery disease and one further patient probably had transient cardiac ischaemia. This is of special interest, because Thannhauser[3] has suggested that a special liability to coronary artery disease is not met with in idiopathic hyperlipaemia. None of the ten cases showed enlargement of the liver and only one had an enlarged spleen. This is again unusual, for hepatomegaly and splenomegaly have frequently been described. Klatskin and Gordon[4] have also reported a patient with hyperlipaemia and recurrent pancreatitis, and suggested that the hyperlipaemia was the cause rather that the consequence of the pancreatic disease.

The cause of idiopathic hyperlipaemia is not known. There are several records of familial hyperlipaemia.[2 5 6 7] Malmros also noted that in one patient excessive fat intake appeared to be a factor. Otherwise there seemed to be no obvious cause. The laboratory findings finally established the diagnosis. The serum, even after fasting, varies from a creamy to a well-marked opalescent appearance. The total lipids are raised. The serum cholesterol is also usually well above normal limits, although in three of Malmros's patients the values were below 300 mg. per 100 ml. Filter-paper electrophoresis shows that not only is there an increase in the chylomicron fraction but also in the β fraction. This may be of importance, for Rosenberg, Young, and Proger[8] have found this fraction raised also in coronary artery disease. Histological examination of the skin xanthomata shows that they do not differ from essential xanthomatosis of the hypercholesterolaemic type. The bone marrow may be found to contain many foam cells.

Treatment is directed towards restoring the blood lipids to normal in the hope of preventing serious arterial disease. Malmros suggests that this may be achieved by a low-fat diet, which, if prolonged, may result in the return of the lipoprotein pattern to normal. In one of his patients it appeared to relieve severe symptoms of angina pectoris and in another the skin lesions disappeared. Not only is idiopathic hyperlipaemia of clinical importance, since treatment may benefit the patient, but it perhaps has a special significance in shedding light on some of the problems of lipid metabolism. The factors controlling the level of serum cholesterol and the method by which the blood is cleared of chylomicrons are not yet fully understood, and it is possible that further investigation of this rare condition will help to clarify these mechanisms.

AFIBRINOGENAEMIA IN PREGNANCY

In spite of the availability of transfusion facilities postpartum haemorrhage is still responsible for many maternal deaths. Among the causal conditions which may not be recognized is acquired afibrinogenaemia complicating pregnancy. This occasionally occurs in patients who have premature detachment of the placenta, the syndrome associated with amniotic fluid embolism, or a long-standing foetal death in utero (most commonly in Rh-negative sensitized women). Acquired afibrinogenaemia complicating pregnancy, although described over fifty years[1] ago and occasionally[2–8] since, is still a rare enough condition not to be mentioned in the obstetrical and gynaecological textbooks. But interest in it is increasing, and in a recent paper published in this *Journal* Barnett and Cussen[7] report two cases associated with abruptio placentae. In both there was evidence of severe retroplacental bleeding before spontaneous delivery of a dead foetus; postpartum hamorrhage occurred with a fully contracted uterus and without any evidence of trauma. It was noticed that the blood shed per vaginam failed to clot, and the diagnosis of afibrinogenaemia was confirmed by the finding that venous blood at the height of the bleeding phase failed to clot within forty-eight hours. Further confirmation was obtained when microelectro-

[1] *Arch. Derm. Syph., Wien*, 1932, **166**, 542.
[2] *Acta med. scand.*, 1954, **149**, 91.
[3] *The Oxford Medicine*, New York, 1949, **4**, part 2, 214.
[4] *Amer. J. Med.*, 1952, **12**, 3.
[5] Harslöf, E., *Acta med. scand.*, 1948, **130**, 140.
[6] Holt, L. E., jun., *et al.*, *Bull. Johns Hopk. Hosp.*, 1939, **64**, 279.
[7] Levy, B. M., *J. Pediat.*, 1946, **29**, 367.
[8] Rosenberg, I. N., *et al.*, *Amer. J. Med.*, 1954, **16**, 818.

[1] DeLee, J. B., *Amer. J. Obstet.*, 1901, **44**, 785.
[2] Dieckmann, W. J., *Amer. J. Obstet. Gynec.*, 1936, **31**, 734.
[3] Moloney, W. C., Egan, W. J., and Gorman, A. J., *New Engl. J. Med.*, 1949, **240**, 596.
[4] Weiner, A. E., Reid, D. E., and Roby, C. C., *Amer. J. Obstet. Gynec.*, 1950, **60**, 379; 1953, **66**, 475.
[5] Williams, J. W., *J. Obstet. Gynaec. Brit. Emp.*, 1925, **32**, 268.
[6] Willson, P., *Surg. Gynec. Obstet.*, 1922, **34**, 57.
[7] *British Medical Journal*, 1954, **2**, 676.
[8] Page, E. W., Fulton, L. D., and Glendening, M. B., *Amer. J. Obstet. Gynec.*, 1951, **61**, 1116.
[9] *Practitioner*, 1954, **173**, 360.

phoresis of the plasma showed absence of fibrinogen bands (unfortunately this test takes about twenty-four hours).

The incoagulability of the blood in these cases is now thought to be due to a rapid depletion of the plasma fibrinogen.[8] This defibrination is probably due to the escape of placental and decidual thromboplastin into the maternal circulation: this converts the prothrombin into thrombin, which in turn converts fibrinogen into fibrin, and the latter is deposited over the endothelium of the blood system, occasionally producing serious visceral lesions. Increased intrauterine pressure caused by the retroplacental clot may force this thromboplastin substance into the maternal circulation. There are also powerful contractions of the uterus and therefore increased uterine pressure in the other conditions which cause afibrinogenaemia. This explanation of the causation receives confirmation from the fact that infusion of human placental thromboplastin can produce a similar syndrome in dogs.[8]

Afibrinogenaemia may occur in different degrees of completeness, and its prompt and effective treatment may stop serious, if not fatal, haemorrhages. When it is associated with abruptio placentae the severe haemorrhage must be dealt with as an emergency, and the obstetrician himself must quickly confirm the existence of this coagulative defect by the methods already described and remedy it by the prompt intravenous injection of fibrinogen, now readily available from the blood banks, supported by massive whole blood transfusions. These measures should, as in the cases described by Barnett and Cussen, restore the clotting mechanism, and this must be achieved before any other surgical treatment is attempted. Tenney[9] has recently suggested that the longer the time between the separation of the placenta and the delivery of the child, the greater the chance of developing afibrinogenaemia, and caesarean section may be indicated if the patient cannot be delivered from below within ten to twelve hours. Afibrinogenaemia associated with foetal death in utero usually manifests itself clinically as a generalized purpura and has to be differentiated from thrombocytopenic purpura. It must be borne in mind that this latter condition may also give rise to severe post-partum haemorrhage in the presence of a well-contracted uterus. It is differentiated from afibrinogenaemia by finding a low platelet count and a normal blood coagulation time. The bleeding usually comes from lacerations rather than from the uterus.

TOBACCO BRONCHITIS AND ANAESTHESIA

Though attention has been focused on smoking mainly because of the likelihood that it is a cause of lung cancer, the habit has other undesirable side effects, notably bronchitis, usually spoken of in terms of its main symptom—the "smoker's cough." The connexion between chronic bronchitis and smoking, always taken for granted, received some confirmation from Palmer,[1] who studied a group of over 400 males admitted to the Middlesex Hospital for operation for inguinal hernia or peptic ulcer. He found that not only was the incidence of bronchitis significantly higher in smokers than in non-smokers, but that the incidence of bronchitis increased with amount smoked.

The effect of tobacco bronchitis on the administration and after-effects of anaesthesia has received some attention in the past.[2,3] Many anaesthetists believe that smokers are more difficult to anaesthetize than non-smokers, and that they are more likely to cough and to develop laryngeal spasm during the administration of such anaesthetics as ether. They also believe that smokers are more likely to have post-operative respiratory complications, the severity of which, other factors being equal, runs parallel with the amount smoked. These ideas now receive additional confirmation from a paper by Green and Bercowitz,[4] who give data obtained from over 4,000 patients coming to operation. The figures they give of the quantity of tobacco smoked, and of the frequency with which these amounts are smoked by various individuals, form an interesting social side-light on the smoking habits of lower-middle-class New York residents. They show, however, just as Palmer did, that bronchitis occurs more frequently in smokers, and that the severity varies with the amount smoked. They state that smoking is four to seven times more common a cause of bronchitis than all other causes combined. So far as anaesthesia is concerned, it seems that a good way of assessing the type and severity of the bronchitis is by noting the character of a spontaneous cough in the anaesthetic room. Unlike the normal test cough, which is dry and clear, the abnormal test cough is generally a heavy "propagated paroxysm," wet or dry. Green and Bercowitz found a clinical correlation between an abnormal test cough and the presence of tracheo-bronchial disease. The abnormal cough was always obtainable before operation in patients who developed serious post-operative chest complications after surgery, while it was generally absent in patients who did not develop these complications. During anaesthesia the liability to laryngeal spasm may be serious, and they quote a macabre case in which an otherwise healthy adult about to undergo an appendicectomy died when he developed laryngeal spasm which could not be relieved: "The surgeon refused to perform a tracheotomy, the anaesthetist failed to remember the specific value of curare." Apart from laryngeal spasm, bronchospasm and bronchorrhoea are other undesirable complications which may occur. The inescapable conclusion is that tobacco bronchitis is a sufficiently serious complication in a patient about to have a major operation for his medical attendants to pay special attention to it. Any alteration in habit must be undertaken sufficiently far ahead to ensure a satisfactory effect, and to judge this a detailed knowledge of the patient's smoking habits and their effects on his respiratory system should be known. Green and Bercowitz point out, somewhat acidly, that such advice should not be dictated by the physician's own smoking habits.

[1] *British Medical Journal*, 1954, **1**, 1473.
[2] Morton, H. J. V., *Lancet*, 1944, **1**, 368.
[3] Lee, J. A., *Anaesthesia*, 1949, **4**, 169.
[4] *Ann. intern. Med.*, 1954, **40**, 729.

DEDICATION OF THE WAR MEMORIAL

ARCHBISHOP OF CANTERBURY AT AN IMPRESSIVE CEREMONY

The Memorial in the Court of Honour of the British Medical Association House in Tavistock Square was dedicated by the Archbishop of Canterbury (Most Rev. Geoffrey Fisher, D.D.) on Tuesday afternoon, November 2. The occasion must have recalled to the older members present the dedication almost thirty years ago by Archbishop Randall Davidson of the Gates of Remembrance which had been designed by the late Sir Edwin Lutyens as a memorial to the 574 members of the Association who fell in the first world war. On that occasion, after the Gates had been dedicated, King George V and Queen Mary were the first to drive through them to open the new House of the Association. The House since then has been extended largely on its northern, southern, and western sides, but the vacant space of the Court of Honour has awaited some great work of art to match the Gates. This has now been achieved by a fountain surrounded by sculptured figures as a memorial to the medical men and women of the British Empire and Commonwealth, nearly one thousand in all, who gave their lives in the second world war.

The service of dedication was simple and moving. It began with a processional hymn, the singing being led by the choir of the Queen's Chapel of the Savoy, and the music played by the band of the Royal Army Medical Corps. The vicar of the neighbouring church of St. Pancras, the Rev. W. P. Baddeley, offered prayer, and a passage was read from the Book of Wisdom by the Moderator of the General Assembly of the Church of Scotland, the Right Rev. E. D. Jarvis, and another from the First Epistle to the Thessalonians by the Rev. A. Drummond Harcus, representing the Moderator of the Free Church Federal Council. Goss's anthem, "I heard a voice from heaven," was sung, and then, on the invitation of Dr. H. Guy Dain, Chairman of the War Memorial Committee, the President of the Association, Sir John McNee, unveiled the memorial plaque and read the inscription:

In Memoriam 1939–1945

In Honour of the Medical Men and Women of the British Empire and Commonwealth of Nations who gave their lives in the Second World War.

This was followed by the sounding of the Last Post, and the Archbishop, who was wearing his Convocation robes, proceeded, before dedicating the Memorial, to give a short address.

The Archbishop's Address

The Archbishop began by saying that he found the dedication of war memorials more and more moving in its significance as time went on. "This Memorial is to those of the medical profession—those names in the Roll of Honour of Members of the Association, and how many more I know not—from all parts of this Commonwealth who gave their lives in the war.

"These doctors were there in the beastly occupation of war, doing only lovely and loving things to ease pain and bring healing. I am told—and I easily believe it—that they did their work in this war with far greater effect than in any previous war. There was better organization, better transport, new treatments, new drugs, and every new apparatus that the devotion and skill of the medical profession had brought within their reach. These men and women ministered to others, and in that ministry they themselves were taken. 'He saved others, Himself he cannot save.' Those words were spoken once to a divine Sufferer. These medical men saved others, themselves they would not and could not save. They very specially have a kinship with Christ on His Cross. Like Him, having the means of salvation of a kind within their skill and knowledge, they would not use it to avoid their own sacrifice, but embraced the sacrifice as a glorious triumph of their calling and of their healing art.

"So these men and women, every one of them, sought and found the fellowship of suffering with Him. Here are the great realities by which we must walk if we will live. We owe so much to these men and women and their like who, giving their all to save this nation and this civilization, bought with the price of their lives a space for repentance and reformation and hope for mankind. Above all, we owe them undying gratitude in that, whether they knew it or not, they keep us from sloth and compel us to face our daily lives in the realities which embraced and enveloped them and the sacrifice which they made.

"For here indeed," the Archbishop concluded, "is the law of life, the law of Christ, the law of God. 'Whosoever shall lose his life and throw it away for My sake and for the gospel's and for the service of others shall keep it unto life eternal.'"

Dedication of Memorial

The dedication was followed by the sounding of Reveille and by a hymn specially written for the occasion: "We praise thee, Lord, for those who gave Themselves at duty's call." After the Benediction and the National Anthem the Chairman of Council, Dr. E. A. Gregg, laid a wreath at the base of the Memorial and was followed in so doing by the President of the Medical Women's Federation, Dr. Annis Gillie. The Roll of Honour in the Members' Common Room in which are inscribed the names of members who fell in both world wars was then inspected. The Roll for 1939–45 contains 542 names.

The Memorial

The Memorial takes the form of a central fountain, with two symbolic heroic-size figures on the west and two on the east side, all in Portland Stone. The design of the bronze fountain jet is based on the shape of the staff of Aesculapius. The four statues have as their themes Sacrifice, Cure,

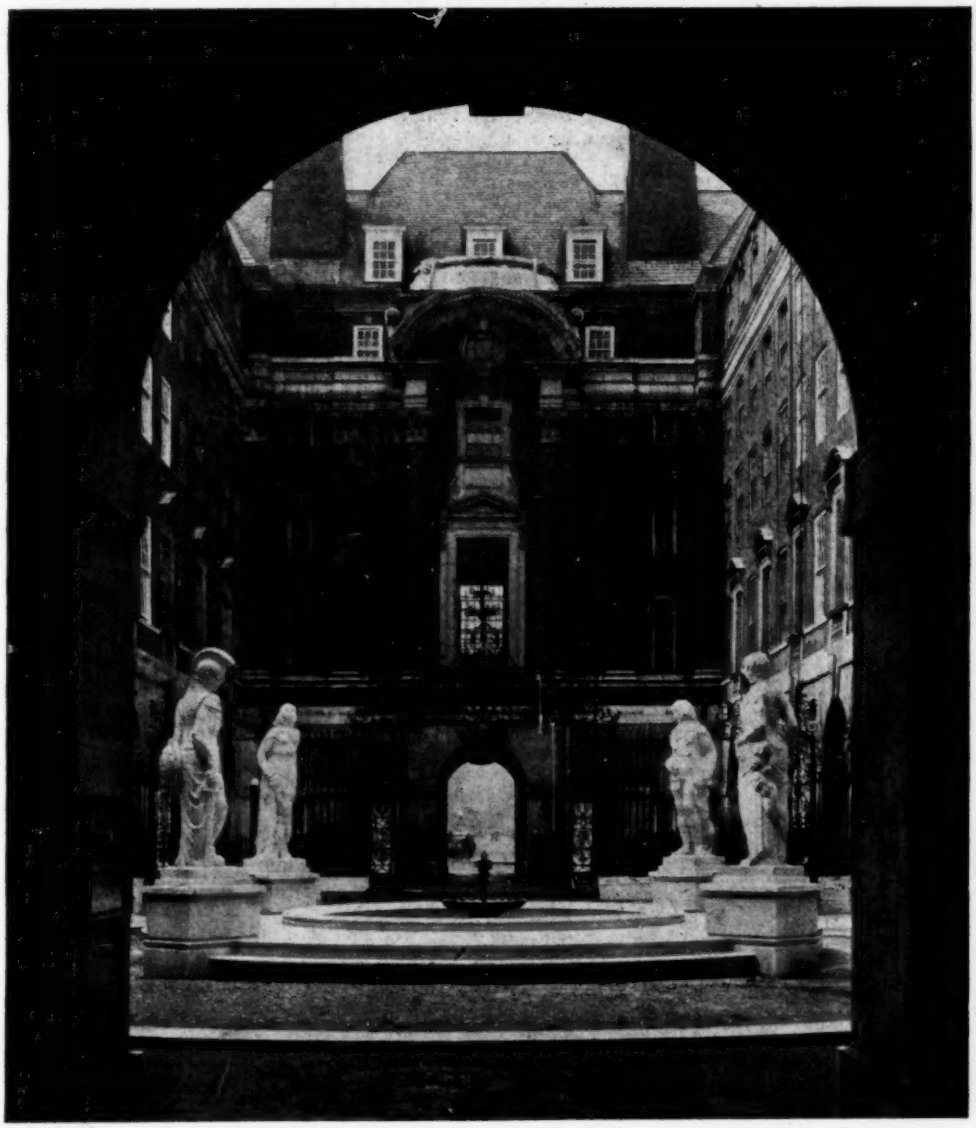
SYMBOLISM OF THE FIGURES

SACRIFICE.—This statue represents Machaon, in a symbolic portrayal of Sacrifice. Machaon, said to have been a son of Aesculapius, was the first recorded medical war casualty. Both a surgeon and a soldier, he fought in the Trojan Wars, circa 1200 B.C. The sculpture shows Machaon in the act of falling, pierced by an arrow in the thigh. At the base of the figure is a sponge for staunching blood, together with a vase for healing ointments. As a link with the Second World War, the shield bears the symbols of Combined Operations.

CURE.—A symbolic figure representing the post-Greek eras of medicine. A lancet is held in the right hand. The composition of the group is completed by two *putti*; one holds a dish for the receipt of blood after "cupping"; the other carries an early drill, used for the operation of trepanning, and clasps the hand of the central figure. At the base of the group, the lore of the herbalists is suggested by the mandrake plant.

PREVENTION.—This figure, of the period of Jenner, is holding an early microscope as a symbol of early research. The composition of the lower part of the group includes the representation of a dog and a sheep, signifying the discovery of the value of inoculation in preventing disease.

ASPIRATION.—This figure is an idealized representation of Motherhood leading forward a child into the future. At the base of the group fruits are introduced to suggest the way to health through the good things of Mother Earth.



The War Memorial from the East. The Gates of Remembrance are visible immediately behind the Memorial.

SACRIFICE

CURE

PREVENTION

ASPIRATION

The sculptor's explanation of the symbolism of these figures is given on the opposite page.

Prevention, and Aspiration; their symbolism is described at the foot of page 1098. The sculptor, whose design was accepted after a limited competition in accordance with rules drawn up by the Royal Society of British Sculptors, is Mr. James Woodford, R.A., who called into collaboration with him Mr. S. Rowland Pierce, F.R.I.B.A. The proposals were accepted by the Representative Body in 1950, and the work of construction began in 1953. The cost of the Memorial has been defrayed from voluntary donations totalling over £8,000 as a result of an appeal by the Chairman of Council, and, in accordance with the wishes of some of the donors, a proportion of the funds has been set aside for assisting in the education of the children of the fallen.

Mr. James Woodford has executed much important sculptural work, including the bronze doors and pylon figures for the R.I.B.A. building in Portland Place, carved woodwork for the *S.S. Queen Mary*, the sculpture on the new building of the Ministry of Agriculture in Whitehall, and many works for the Imperial War Graves Commission. But perhaps he is best known for designing and modelling the "Queen's Beasts" and other parts of the decorative scheme for the Coronation Annexe to Westminster Abbey. He received his early training at the Nottingham School of Art, and one of his later works is the bronze statue of Robin Hood, with groups and reliefs, on Robin Hood Lawn, Nottingham. In association with Mr. Rowland Pierce he has carried out some very fine work on public buildings in Norwich, Hertford, and elsewhere. Mr. Pierce is a Vice-President of the R.I.B.A., and is actively engaged on town planning.

Many expressions of admiration were forthcoming from those attending the ceremony, not only for the detailed execution of the work but for its general conception and effect. Some recalled an earlier essay of the B.M.A. in sculpture, when it commissioned Mr. Jacob Epstein to design some above-life-size figures for the exterior of the Association's new house in the Strand in 1908. Whatever may be said in criticism of the new memorial or its symbolism it is hardly likely to create the furore in the sensational press that the Epstein figures did; but it is a very fine piece of work which grows upon the observer as he contemplates it.

Those present at the ceremony included many of the next-of-kin of the medical men and women who lost their lives in the war; also the Minister of Health (Mr. Iain Macleod, M.P.) and the Parliamentary Secretary (Miss P. Hornsby-Smith, M.P.), and the Mayor of St. Pancras. Many of the distinguished men and women attending the ceremony came as representatives of medical institutions and organizations in Britain and the Commonwealth. The principal officers of the Association were present, the procession being headed by the President and the Chairman of Council. The heads of the Medical Departments of the Services were in attendance, also representatives of the Overseas Branches of the Association and Medical Associations of the Commonwealth. Mr. James Woodford, the sculptor, and Mr. S. Rowland Pierce, the architect, were presented by Dr. Dain to the President.

RESEARCH IN GENERAL PRACTICE

The Royal Statistical Society's study circle on medical statistics met at Westminster Hospital Medical School on October 26 to hear and discuss a paper by Dr. JOHN FRY, himself a general practitioner, on research in general practice. The chair was taken by Dr. G. F. ABERCROMBIE, chairman of the council of the College of General Practitioners.

Before describing his investigations in his own practice, Dr. FRY gave a brief account of the work of a general practitioner, making it clear that the application of statistical analysis in such circumstances was bound to be of an elementary type. In any case he believed that statistics were less important in general practice than in any other branch of medicine. The difficulty of getting reliable statistics under working conditions was closely related to the difficulty of accurate record-keeping, which should be simplified as much as possible, and must be capable of being fitted in with the day's work. Neither were possible without secretarial help, though this did not need to be whole-time. Diagnosis in general practice was often symptomatic and inexact by hospital standards. Other important limitations were that any research done should not interfere with the doctor–patient relationship, and that the patient should be put to no risk from the investigations. He thought that general practice presented a practically virgin field for research, particularly into acute respiratory infections, familial diseases, and chronic diseases.

Causes of Attendance

After describing the methods of record-keeping he used in his own practice, which was in a middle-class residential suburb in south-east London, among people in social classes 3 and 4, Dr. Fry went on to give an account of some of his observations over the three years 1951–3. During that time the rate of attendances per patient varied from 3.2 to 3.4. The number of women patients in his practice exceeded that of men, and women attended more often than men. The attendance rate was highest in the age-group 40 to 50, the increase being almost wholly among women, especially at the time of the menopause. On the basis of their attendance rate, the healthiest age group was from 10 to 20 years, and patients of more than 70 needed the most attention from their doctor. The age group from 0 to 4 years did not need as much attention as those in the 50 to 60 decade.

In all the three years under review upper respiratory infections had been the commonest conditions seen, followed by acute and chronic chest infections, digestive disorders, neurosis, and skin diseases. The first two groups of illnesses accounted for 25% of all attendances. In his practice he had seen only one case of rheumatic fever in eight years. There was little sex difference in the incidence of disease, except in patients with neurosis, in which women exceeded men by 2 to 1. He thought that the diagnosis of neurosis was very difficult to make and notoriously unsatisfactory, but less liable to error in general practice, because the general practitioner knew his patients and their familial and social environment well. Respiratory diseases showed a rise in incidence at 5 to 10 years, but the incidence was constant from 10 to 50 years, after which it rose again in elderly people, due almost entirely to chronic bronchitis. In his experience children who had recurrent colds between the ages of 3 and 8 years, if left alone, seemed to develop some kind of immunity. In the past they had often undergone tonsillectomy, but if the parents could be prevailed upon to adopt a purely expectant attitude, operation might often be avoided.

Dr. Fry spoke highly of the facilities for radiological and pathological examination which were available at his local hospital. The number of patients he referred for *x*-ray investigation was about 5 to 6% of his whole practice, and for pathological tests about 5%. The tests were mostly blood counts, examinations of throat swabs, and urine and faecal examinations. There had been an increase of from 6.9 to 10% in patients he referred for consultant opinion.

The Commonest Diseases

The commonest organic diseases were acute and chronic bronchial and pulmonary infections, hypertension, acute backache and lumbago, migraine, peptic ulceration, and coronary artery disease, in that order. Rheumatic valvular disease of the heart was uncommon, and in his opinion was dying out. The hypertension that he saw was almost invariably benign, and often was discovered fortuitously: he did not see many patients with headaches or renal failure from

this cause, and he took care not to tell the patient with such benign hypertension that his blood pressure was high. He believed that medical treatment, and not too much of it, was very adequate for most cases of peptic ulcer, under which the disease did not seem to cause much trouble to the patient.

He concluded with a plea for research in general practice to be undertaken as a group study, which he thought could best be done under the auspices of the College of General Practitioners.

Discussion

In the discussion which followed, Dr. VERA NORRIS said that she felt that undergraduate medical students were being taught about diseases which were not met with in practice, but only inside hospital. She thought this was a good reason for a revision of the curriculum. In reply Dr. FRY said he thought that undergraduates should receive a good grounding in general medicine, but that they should see something of the general practitioner at work. Some medical schools already included a week or two of attachment to a general practitioner in their curriculum.

Another speaker wondered whether the different attendance rates at different ages which Dr. Fry had described might not be due to the fact that those patients who were at work and without family responsibilities might have more time in which they could consult their doctor. Dr. FRY said that in his practice high attendance rates were often shown by parents who were particularly worried about their children. In his opinion the attendance rate of a particular patient depended on his personality.

Another speaker suggested that the general practitioner's statistical year should be from June to June, so as to include a complete winter from October to April.

Answering other points from the floor, Dr. FRY said that the advantages of research to the general practitioner were, first, in stimulating and maintaining his interest in his work, and, secondly, that from it might evolve new lines in the management of certain illnesses.

ST. JOHN AMBULANCE BRIGADE

SURGEONS' WEEK-END CONFERENCE

[FROM A SPECIAL CORRESPONDENT]

The St. John Ambulance Brigade held a week-end conference for their surgeons and nursing officers at B.M.A. House on October 30 and 31. On the afternoon of the second day certain of the fundamental aspects of first aid were considered. Major A. C. WHITE KNOX was in the chair.

During the past few months doubts have been raised about the standard teaching on two very important problems of emergency casualty treatment. These are the treatment of shock and of the unconscious patient. Letters have appeared in the *British Medical Journal* suggesting that it is better to keep the shocked patient cool than to attempt to warm him. In support of this view it is argued that the apparent coldness of the patient is due to reflex vasoconstriction, which ensures an adequate blood supply to the vital organs. Attempts to heat the patient and produce vasodilatation would be harmful if successful, the argument runs, as the blood to these structures would be reduced. This opinion does not take into account the fact that the shock process is, in the absence of haemorrhage, harmful rather than compensatory.

Shock and the Unconscious Patient

Discussions on shock are always beset with one great difficulty, that of defining and classifying degrees and varieties of shock, and the Conference was unable to advance any new principle to simplify this problem. The position with regard to treatment was made clearer, however, when a member pointed out the fundamental difference between the casualty surgeon and the hospital accident service. The duty of those engaged in first-aid work was to preserve life in order that the injured man might receive treatment in hospital, he said. The treatment of shock was the task of the hospital resuscitation team; resuscitation must not be attempted in the field, for it was one of the lessons of the last war that second attempts at reviving a collapsed patient were often unsuccessful. Hence the first-aid treatment of the shocked patient was the prevention of further collapse, not the treatment of the shocked state itself. As cold was a recognized factor in the production of shock it was reasonable to prevent further heat loss. In his weak, disoriented state the shocked patient had poor control over his heat-regulating mechanism and so must be helped by the first-aid worker. Deliberate attempts to heat the patient had no part in treatment. This was, in fact, the teaching of the St. John First Aid Manual.

In the press there appeared a short time ago an account of a lecture apparently criticizing the standard first-aid treatment of the unconscious patient. The First Aid Manual advises the elevation of the head and the application of cold compresses to the forehead. The reason given for these measures is that they may combat the lethal complication, cerebral compression. The lecturer quoted was of the opinion that the most dangerous hazard to the unconscious patient is not cerebral compression but the aspiration of blood, mucus, and vomit with resultant bronchopneumonia. In the absence of an adequate cough reflex the only effective way of preventing aspiration, it was suggested, is by turning the patient on to his side, or even completely prone, with the head depressed. Fluid in the oropharynx will then flow out of the mouth by gravity instead of into the trachea.

The reaction of the conference to this suggestion was, at first, hostile; many considered the supine position, as advised in the Manual, the best. The chairman, however, was of the opinion that the matter should be further discussed and that the accepted teaching might require modifying. The conference assented to this. This was a wise decision; the dangers of aspiration of fluid into the respiratory tract in the unconscious patient are well known. They are far greater than the risks of cerebral compression, which sets in only after several hours and for which only operative treatment is of avail.

After a short discussion on the advisability of training first-aid workers in the use of the hypodermic syringe, the conference was adjourned.

Reports of Societies

THE MANAGEMENT OF ADVANCED CANCER

One of three themes chosen for "summing up" at a meeting of the Section of Medicine of the Royal Society of Medicine on October 26 was "The Management of Advanced Cancer." The others, not reported here, were "The Uses of Radiotherapy and Chemotherapy in the Treatment of Reticuloses" and "The Use and Limitations of Skin Tests in Asthma." Sir HENRY COHEN was in the chair.

Dr. RICHARD ASHER (Central Middlesex Hospital), in a speech full of apt quotations, said that in contemplating treatment of advanced cancer one must ask several questions. How much distress was the patient suffering? How much relief could the doctor give? And how much distress would the patient suffer from treatment? Extensive surgery was justified if the mode of death without it was distressing, as in carcinoma of the oesophagus; on the other hand, carcinoma of the lung was so common that cases of doubtful

operability were best not referred to chest surgeons, who should concentrate on the treatment of early cases. Palliative surgery depended on the severity of symptoms: one might, for instance, operate to relieve the symptoms of jaundice, but would not lightly advise a colostomy. Radiotherapy was undoubtedly of great value, but had some disadvantages. Patients often guessed what was wrong if they were treated in this way. Reactions were common, especially in carcinoma of the lung, where superior vena caval obstruction was probably the only absolute indication. In the leukaemias there was a real danger of treating the blood count rather than the patient. In disseminated cancer of the breast or prostate extensive endocrine surgery might be dramatic, but was as yet an advance in knowledge rather than in therapy. Again there were disadvantages: the operations were extensive, the patient became dependent on a scarce and expensive drug, and the brief improvement might mean two downhill stages instead of one.

Medical management, continued Dr. Asher, consisted largely in making the patient's journey to the grave tolerable and smooth. The fewer investigations that were done the better. It was probably best not to tell the patient the diagnosis, and even the relations might be kept in ignorance till a late stage, so as to avoid the gloom attendant on an incurable disease. Minor symptoms should be treated energetically. Morphine, by mouth rather than by injection, should be given, but need not necessarily be increased, as pain often subsided terminally.

Sir STANFORD CADE (Westminster Hospital) commented on the aptness of the title: it was important to stress management, because this might mean no treatment at all. His aim was not to prolong but to preserve life with the minimum possible symptoms. The extent of surgical treatment depended on many factors, and prejudice on the part of the surgeon should not enter into the matter. Major surgery was by no means better surgery, but in selected patients it might be justifiable "to operate on the inoperable." Sir Stanford then showed examples where extensive multivisceral surgery had not only prolonged life but had resulted in considerable happiness.

Radiotherapy was even more important than surgery, said Sir Stanford, because whereas only 12–15% of patients were treatable by the latter most patients could be treated by this means. Supervoltage therapy was comparable to multivisceral surgery, and caused far less punishment to the patient than conventional radiotherapy; here again dramatic improvement could be obtained. Of 70 patients with advanced and disseminated cancer of the breast treated personally by adrenalectomy and oophorectomy, 30 had been grateful for the operation. Similar results were reported after hypophysectomy. Survival was not the point; relief of symptoms was the major consideration, and if the surgeon had even a slender chance of achieving this he was morally bound to operate. Chemotherapeutic agents such as R 48 might be of value in conditions other than reticuloses—for instance, in myelomatosis, malignant melanoma, and carcinoma of the lung. The use of radioisotopes, particularly radioactive gold, opened up new fields, especially as these were now being given locally by intra-arterial injection. Morphine was not a form of therapy, but a means of helping the patient to die; it should be reserved for the terminal stages.

LEISHMANIASIS: NEW VECTOR IN KENYA

At a meeting in London of the Royal Society of Tropical Medicine and Hygiene on October 21, Dr. R. B. HEISCH, of the Medical Research Laboratory at Nairobi, presented evidence that a sandfly from the ventilation shafts of white-ant hills had probably been the vector responsible for a severe outbreak of leishmaniasis in Kenya. This sandfly had not previously been known to science.

Dr. Heisch described the investigation of the epidemic, which occurred in the Kitui District. There were some 3,000 cases, mostly in children, with a preponderance of males. Their distribution did not point to a village infection, since in any particular village only a few cases occurred, which suggested that the infection might have been contracted in the bush. In the attempt to identify the vector and an animal reservoir about 5,000 sandflies were examined, and hundreds were dissected with meagre results; 330 gerbils, 30 mongooses, and a number of other animals proved negative for *Leishmania*, though two hamsters, inoculated with organs from groups of gerbils or mongooses, became infected, but here there was a possibility of laboratory cross-infection. Several new species of *Phlebotomus* were observed, and one, provisionally known as *Phlebotomus* (*Sergentomyia*) sp. nov. 2, was probably the vector. It was found in the ventilation shafts of termite hills, and was widely distributed in the area. It persisted for several months after the rains, and was the only one of the anthropophilic species found naturally infected with leptomonads in the anterior part of the mid-gut. But attempts to infect it in the laboratory failed. The evidence against other species was poor.

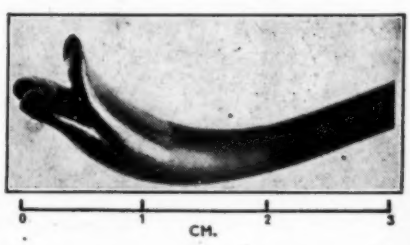
The new sandfly apparently bit in the open, went on Dr. Heisch, and did not haunt human dwellings, and it seemed probable that persons were infected while resting near termite hills. It followed that treatment of houses with insecticides would probably be ineffective in prevention. In this outbreak the disease had proved very resistant to treatment.

In the discussion, Dr. L. E. NAPIER made the point that in India the age distribution of cases, when whole populations were examined, was much the same as in Kenya. The impression that the disease is one of adult life in India was incorrect.

Preparations and Appliances

URETHROTOMY GUIDE

Mr. A. WILFRID ADAMS, surgeon-in-charge, genito-urinary department, United Bristol Hospitals, writes: The opening of the bulbous urethra over an ordinary urethral dilator leaves much to be desired in ease and efficiency. Hence the guide here illustrated has been designed for the purpose. Special features are a spoon-shaped handle enabling the assistant to hold it steady with ease; the obtuse angulation of the shaft, 2 cm. from the end, protrudes the bulbous urethra ventrally, bulging the perineoscrotal junction; the expanded tip has a shallow vertical cleft and a deep transverse one (see photograph).



A 3-cm. incision is made—two-thirds on the scrotum, one-third on the perineum—down to the bulging urethral wall. Before entry into the lumen, however, lateral traction stitches can be inserted correctly, thanks to the tiny half-circle needles traversing the guiding transverse groove. This and the vertical groove are palpable and sometimes faintly visible through the stretched urethral tube. After transfixing the lumen on one side, the stitch is lightly held whilst another is inserted on the opposite side, leaving a millimetre or so between them. The knife then cuts down the vertical groove—kindly suggested by my colleague, Mr. J. P. Mitchell—between the traction stitches and nicks the urethra at the ends of the 2-cm. incision before severing the intact mucosal bridge. Sure entry through a neat wound results.

The Genito-Urinary Manufacturing Company, of London, are kindly making the instrument.

Nova et Vetera

LETTERS FROM THE CRIMEA

It is probably true to say that a century ago first brought to light the necessity for a revision of the medical arrangements in military operations. For the Crimean War, with its muddle-headed planning and red-tape regulations, led to such an enormous loss of combatant personnel that the whole approach to the question of the preservation of health among the fighting men (apart from treating them for wounds) had to be drastically revised. The medical breakdown in that campaign was found by the Royal Commission on the Crimean War to be due to the then existing system and not to the surgeons in the field, who nobly did their utmost for the men under their care despite their lack of drugs, ambulances, proper food, bedding, and nurses. The part played by Miss Nightingale in attempting to deal with the sick and wounded at the Base Hospital at Scutari is well known, but perhaps not so much attention has been given to the surgeons on the battlefield.

A remarkable collection of old letters written by a young assistant surgeon from Balaclava Hospital, and from the camps before Sebastopol between November, 1854, and February, 1856, shows vividly the terrible difficulties under which they laboured.[1] Men with cholera, dysentery, fever, and the wounded were all mixed together without beds or bedding, and the sick lay on the muddy floor in their own clothing. There were no nurses, but two old soldiers, untrained, acted as orderlies and attempted to look after the needs of the patients; they were chiefly engaged in burying the dead rather than looking after the living.

According to the Medical Code the surgeon in charge had to draw up a daily diet rota for his patients despite the fact that the items he specified simply did not exist. These records had to be kept to satisfy regulations, and it was largely because of protest against the absurdity of this procedure that the writer of the letters was sent up to the front, where he encountered such appalling conditions that he wrote:

"We are all overworked, and the men are in fact dying from fatigue and bad food. It is a great shame that we have such bad food. They give us salt pork or beef, in which there is but little nourishment, five days out of six, and then the fresh meat is what no one would eat in England, this with hard biscuit is all we have to live on except some green unground coffee, and rum. Fancy a poor fellow coming home having been twelve hours in the trenches, cold and perhaps wet through—he has first to get a fire to cook his meat, and make some exceedingly bad coffee, and finally to sleep in a damp tent on the ground with one or at the most two blankets. Can you wonder at this being enough to kill any man however strong? And I have rather underdrawn the picture. We are sadly deficient in medicines and medical comforts."

Sad Havoc

To a late fellow student at St. Thomas's Hospital he wrote on December 22, 1854:

"I have not seen very much surgery yet, for as soon as a man is wounded he is shipped off to Scutari if he can bear the journey. I was saying to Hawkins the other day that it was very provoking not to know the end of one's cases. He replied, 'Oh, do you see those mounds of earth over there?—that's the end of all the cases!' Which is true, for if a man is too much hurt to be sent to Scutari he almost always dies up here—a tent not being the best place for a man with a bullet through his chest. Disease is making sad havoc amongst our troops; medicine is of little or no use, it is the provisions that are the cause of it. We lose at least 500, and I should think 1,000 men a week from disease; they are sent to Scutari and never seem to return."

And on January 1, 1855:

"Last week I had two letters from Scutari—the first was from a man who had *not* been out here, he described it as very uncomfortable, and a horrid place; the other was from Hervey Ludlow who *has* been out here and sent to Scutari invalided—he writes that it is a sort of Paradise compared to Balaclava. Now you must understand that *we* consider Balaclava a place where men live well and are able to keep themselves dry, and have no trench work—so from this you can perhaps gather what an enviable situation the Camp is. Four weeks ago all the Regiments in this, the 3rd Division, had their full compliment of Assistant Surgeons, and now few have more than one, the rest have all knocked up.

"The treatment of disease is very much simplified out here as we only have about five drugs, they are—Morphia, Quinine, Dover's Powder, Tartarized Antimony, and Calomel: sometimes we get a little Opium, but it soon goes. We have no tea, arrowroot, or any other thing thought to be indispensible in a London Hospital . . . now, fancy with things in this state having to treat bad cases of dysentery, fever, frostbite, gunshot wounds, etc.—it is all but impossible, you would say; at all events it is most disheartening, especially when you consider we have no nurses, and most men are covered with vermin.

"I called in to see a friend living a few tents from me, a young Assistant Surgeon named Erskine, who is ill. I found him dreadfully weak with nothing to eat but salt pork. I had fortunately bought some Essence of Beef when last in town in case I should fall ill myself; this I gave to him with some preserved milk. I hope he will get better for he is a nice fellow, but it is awful work falling sick up here, the Authorities seem to have no feeling, and have a particular aversion to allowing Surgeons to go to Scutari as they are so much wanted up here.

"Last night in my Brigade we could not muster 900 men out of three Regiments each of which came out 1,000 strong. My duty has been very unpleasant as I often have to decide whether some 60 men are shamming or really fit to go to their duty. If at home they would all have been in the Hospital weeks ago, but I am often obliged to send them to duty with a harsh word when I feel inclined to cry for the poor fellows—such is War."

Rotten Arrangement

On January 24, 1855, he wrote:

"There is still an immense deal of sickness, but I don't think it is increasing much—to-day we have neither Quinine, nor Opium, very useful in dysentery. The Medical Department have no power and is quite dependent on the Commissariat—Government seeming to think a corrupt clerk is more to be trusted than a Surgeon . . . the whole arrangement is rotten in the extreme."

In June, of the trench work, he wrote:

"It's all very well to call Doctors 'Non-combatants,' but when they stand a better chance of getting shot than almost anyone else—they being obliged to run about from one end of the works to the other—I think they ought to have some credit for it, but we are an ill used race, and therefore can't expect it."

As an example of the muddle of those days:

"Lord Raglan wrote to Smyrna the other day for 12,000 leeches; they came up in stoppered bottles, and were therefore all dead. You may think it strange Dr. Hall had not got some long ago (so do I), I suppose he thinks they, like Chloroform, are unnecessary."

This reference to chloroform, which was but recently invented, was due to the famous memorandum issued by the Director-General condemning its too frequent use because it was considered the cries of the patient undergoing an operation were an indication to the surgeon of the absence of syncope, and that pain had a stimulant effect which assisted recovery.

As a result of public reaction to these scandals, as well as of the tremendous advances made in medicine, dietetics, and transport, the loss of life in later wars due to disease and neglect has been much reduced. Wars are always cruel, and it is the pride of the medical and nursing professions that they give of their best service to the alleviations of the sufferings of the fighting men. Nevertheless the unnecessary and gross loss of life of a century ago due to autocratic inefficiency is a reminder of the heroic efforts then initiated to overcome indifference.

[1] The letters quoted were written by Surgeon Lieutenant-Colonel E. M. Wrench, F.R.C.S., who was apprenticed at the age of 14 to St. Thomas's Hospital in 1847. Some of his Crimean reminiscences appeared in the *British Medical Journal*, 1899, **2**, 205, and 1908, **2**, 388.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Cyanacetic Acid Hydrazide

SIR,—In a letter from Dr. M. O. J. Gibson (*Journal*, September 18, p. 704) it was erroneously stated that cyanacetic acid hydrazide ("reazide") was being tried clinically under the auspices of the Medical Research Council. In reply to an inquiry as to the source of his information, Dr. Gibson explained that he had received it in a letter from the Medical Research Department of S. Maw Son and Sons Ltd., the manufacturers, which contained the following statement: "Reazide is on major clinical trial at thirteen of the very large T.B. hospitals under the auspices of the M.R.C. and to date the results appear to be most encouraging, especially in cases of patients who are resistant to I.N.A.H., and it has even proved efficacious in cases of complete resistance to I.N.A.H., streptomycin, and P.A.S."

While Dr. Gibson is, of course, entirely blameless in the matter, the inference which would naturally be drawn from the firm's statement to him is that reazide is being tested clinically under the auspices of the Council: this would be entirely incorrect. The Council has in fact accepted the recommendation of its advisers on tuberculosis that, in the light of the evidence of laboratory tests arranged by the Council (Barnett *et al.*, *Journal*, July 3, p. 301) and of other reports, it would be premature for them to arrange clinical tests—all the more because of the risk that reazide may cause the emergence in patients of strains of *M. tuberculosis* resistant to isoniazid as well as to itself.—I am, etc.,

HAROLD HIMSWORTH,
Secretary, Medical Research Council.

London, S.W.1.

Low-lying Placenta

SIR,—In the discussion on the risks of surgical induction of labour in the leading article in the *Journal* of October 9 (p. 855) the danger of separating a low-lying placenta is dismissed with the statement that "this complication could be avoided by preliminary placentography." My experience during the last ten years, during which time I have witnessed three torrential haemorrhages following attempted surgical induction of labour when placenta praevia was unsuspected, prompts me to dilate a little on this subject.

A placenta praevia is sometimes malformed; the part of the chorion frondosum which persists in the lower segment may be relatively thin and therefore difficult to demonstrate by *x*-ray. Such was the case in three patients admitted to the maternity unit at St. John's Hospital, Chelmsford, with ante-partum haemorrhage, during the last three years. In the first patient the placenta was situated in the upper segment, but one of several thin succenturiate lobes was praevia. The placenta was bipartite in the second case, the praevia portion being the thinner. In the third case the placenta was very large; the thicker upper portion was inserted on the posterior wall in the upper segment and a thin layer of placental tissue covered the posterior wall of the lower segment, internal os, and part of the anterior wall of the lower segment—an incomplete placenta membranacea. All three observations were made at caesarean section after examination under anaesthesia. I respectfully submit, Sir, that neither the clinical observation that the foetal head is engaged, nor the radiological demonstration of a placental shadow in the upper segment, should be taken as conclusive evidence that placental tissue does not overlie the internal os.

It is a sobering thought that uterine sinuses, into which blood is poured from four large arteries, are in danger of being opened whenever a finger is passed through the cervix during pregnancy, no matter what the radiological appearances may be, and if we perform our surgical inductions with this in mind the purpose of this letter will have been achieved.—I am, etc.,

ANTHONY C. PEARSON.

Chelmsford.

Acute Myocardial Infarction

SIR,—In the paper entitled "Anticoagulants in Coronary Disease," by Drs. A. Rae Gilchrist and John A. Tulloch (*Journal*, September 25, p. 720), the statement is repeatedly made that "only in retrospect are there 'good risk' cases of acute myocardial infarction." Although the assertion is made with the conviction commonly attending the recital of a truism, the authors present no statistics of their own or of other investigators to substantiate this unwarranted claim. Drs. Gilchrist and Tulloch have not thus far reported the results of conservative treatment without anticoagulant drugs in "good risk" patients with acute myocardial infarction. Nevertheless, they advocate the administration of these agents in such patients because "even in the mildest cases a thrombo-embolic episode can cause disaster" and "one myocardial infarct may follow on another without the slightest warning, even within a few days of the original attack."

To assume that "good risk" cases exist only in retrospect clearly infers that the occurrence of complications and death is so common in this group that the physician is unable to foretell the probable outcome in any case until recovery has occurred. This view regarding the "unpredictability" of acute myocardial infarction has found its way into most textbooks on heart disease and has been responsible for unjustified pessimism in prognostication in this disease. We have recently reported the results obtained in 122 "good risk" cases of acute myocardial infarction which were treated without anticoagulant drugs.[1] The decision to withhold anticoagulant therapy was made at the time of the first examination. Only 6 of the 122 patients died during the period of hospitalization, the mortality rate being 4.9%. The death rate for 119 patients surviving beyond the first 48 hours of the attack was only 2.5%. Analysis of the causes of death revealed that the preventable mortality, under ideal anticoagulant therapy, would have been at most 0.8% in this group of patients. Clinical thrombo-embolic phenomena occurred in only four patients, an incidence of 3.3%. In two of the four patients diagnosis of the complication was only presumptive. Not a single instance of cerebral or peripheral arterial embolism was encountered in the entire series. Of the 122 patients, 108 had an uneventful course without complication from onset to discharge. These findings hardly seem to justify the attitude of Drs. Gilchrist and Tulloch with regard to prognostication in "good risk" cases. Moreover, since the incidence of haemorrhagic complications and death due to anticoagulant drugs, even when prescribed by the most competent investigators, appears to outweigh any benefit which such therapy may confer in milder cases, no acceptable basis can exist for its routine use in the "good risk" patient.—I am, etc.,

HENRY I. RUSSEK.

Staten Island, N.Y.

REFERENCE

[1] *Amer. J. med. Sci.*, 1954, **228**, 133.

World Population

SIR,—Your general article on the above subject (*Journal* October 9, p. 865) is, I am sure, most valuable in pointing out the possibilities of error in assessment of the increase in world population, and the symposium on "The Number of Man and Animals" held on September 24 and 25 by the Institute of Biology may "help to damp the ardour of the prophets" as well as "emphasizing the degree of our ignorance on all population problems." It does, however, seem remarkable how far we have to progress before we come to the conclusion, "It is impossible to predict the future with any degree of certainty."

"For now we see through a glass darkly." To improve the accuracy of our facts is fundamental and to continue to

pursue the problem of catering for the world's food supply in spite of the complexity of the factors is vital, but may I make a plea for a more optimistic outlook? Nature's way of controlling the size of the population by starvation may be true in nature, and a principle on these lines in the case of man was put forward by Malthus 150 years ago. He held that there was a universal tendency of the population to outrun the means of subsistence, and was most pessimistic in his outlook on the future of mankind, but then he had omitted many important factors in his reckoning, one of which was that every addition to the population means not only another mouth to feed but also another pair of hands to work with and another brain to think with. The food production of the world may be capable of development beyond any limit yet conceived of by man. He must use not only all the power and resources at his command, but also the more fortunate nations must develop the spirit of sharing their surplus food with those less fortunate in geographical distribution.

There is even less cause for pessimism when we look into the future of mankind if we build on spiritual values. Let us have a little more faith to see God in his works in spite of conflicting evil influences. This will give us hope, and then we can put Christian principles into practice so that the fruits of our labours may benefit others (love). "But now abideth faith, hope, love, these three: and the greatest of these is love."—I am, etc.,

Norwich. G. K. McKEE.

Pain on Swallowing

SIR,—Some time ago I called on a friend who was suffering from acute tonsillitis. He was complaining of severe pain on swallowing and asked me if I could do anything about it. He had been told to take small sips of fluid at a time, but this did not relieve the pain. I then recollected some advice given me many years ago by an old general practitioner whose name, unfortunately, I no longer remember. The advice is simple and consists of taking a very large mouthful of the fluid to be swallowed—as much, in fact, as one can hold in one's mouth—and then swallowing the whole in one effort. This method, of course, applies mainly to fluids, but it gives very considerable relief from pain.

I have had the opportunity of trying it in a number of cases of sore throats, as have also several of my general-practitioner colleagues, usually with considerable relief from pain. Some of my E.N.T. specialist colleagues have also tried it, with success, after tonsillectomies. As this method does not appear to be generally known and as it applies to a condition met with very frequently, I think it may be worth while to call attention to it.—I am, etc.,

London, S.W.15. J. KOHN.

Flourpaper Tuberculin Jelly Test

SIR,—The value of the tuberculin test is at last coming to be increasingly recognized in this country, thanks to no small extent to the work of Dick[1] and the Medical Research Council's National Tuberculin Survey.[2] In that important work, 94,000 children were tuberculin tested using the jelly technique in most cases, and it is unlikely that such a large-scale inquiry would have been so readily accepted if the Mantoux test with its unwelcome needle had been necessary. It is therefore unfortunate that the flourpaper-jelly test has fallen into disrepute, but the work of Coles,[3] Frew,[4] and now Caplin and his colleagues[5] points inescapably to the conclusion that this method of tuberculin testing is not sufficiently reliable for survey work.

Earlier this year, following a tuberculin survey in this town, I had occasion to visit some 45 families where a positive flourpaper-jelly test on a junior schoolchild had led to a search for an infectious case of pulmonary tuberculosis. I took the opportunity to corroborate the jelly test with a Mantoux test (10 T.U.), and found that no less than 12 of these children had, in fact, a negative Mantoux reaction at that strength. In view of this finding it was decided that the jelly test was not sufficiently accurate to conclude that a schoolchild with a positive reaction was infected with tuberculosis, and it has been abandoned for survey purposes in this town. At present, school entrants are still being jelly-tested, but only as a "screen" to recommend seemingly positive reactors for Mantoux testing.

Local health authorities wishing to offer B.C.G. to their tuberculin negative school-leaving children cannot reasonably use the jelly test as a standard tuberculin reaction. Mantoux testing involves the unpopular needle, and to be correctly carried out requires two strengths of tests read at inconvenient intervals afterwards. An alternative to this established tuberculin test is the new multiple puncture test with the "Heaf gun." The reported evidence on the degree of accuracy of this test is, however, scanty. In view of the widespread lack of confidence in the flourpaper-jelly test, the importance of giving B.C.G. to school-leavers, and the increasing importance of the tuberculin test in diagnostic surveys, it is a matter of some urgency to evaluate the "Heaf gun" as speedily as possible.—I am, etc.,

Bournemouth. W. H. TATTERSALL.

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1 *British Medical Journal*, 1950, 2, 141 and 1333.
2 *Lancet*, 1952, 1, 775.
3 Ibid., 1952, 2, 927.
4 *Brit. J. Tuberc.*, 1953, 47, 68.
5 *British Medical Journal*, 1954, 2, 895.

Ultra-violet Fluorescence of the Tongue

SIR,—This phenomenon, described by van den Bergh,[1] has been more recently examined by Tomaszewski,[2] and observations have been extended to Bantu subjects by Squires.[3] Tomaszewski found that in a series of 214 healthy European subjects of all ages a red or yellow-red fluorescence was present in 175 (82%); Squires found fluorescence in 430 (49%) of a series of 873 healthy young Bantu, and in 26 (59%) of 44 South African European children and adolescents. Tomaszewski noted that the administration *per os* of penicillin and other antibiotics abolished fluorescence within a few days; with the cessation of treatment, fluorescence reappeared, also after a few days. He concluded that the phenomenon was due to the production of porphyrins by penicillin-sensitive micro-organisms, although he was unable to identify the organisms responsible. Whilst his observations on the effect of penicillin have been confirmed, it is felt that, on account of the following observations, his conclusion as regards the role of micro-organisms may not represent the entire story.

First, it was observed that of a small control series (20) receiving no penicillin 7 also showed spontaneous waning, disappearance, and waxing of fluorescence over periods of a few days. A large series (1,058) was then examined at three-monthly intervals for over a year; of these, 438 (40%) exhibited similar changes. Secondly, cultivation of scrapings from fluorescent tongues on a variety of media has not produced any fluorescent products, although it may be that, if the fluorescence is indeed due to bacterial action, the phenomenon occurs only when such organisms grow on the tongue, or that they fail to grow *in vitro*. Finally, the fluorescence is not always red; of a recent series of 148 Bakgalakgadi and bushmen of the Kalahari, 50 exhibited fluorescence. Of these, 8 showed, instead of the usual red, a leaf-green fluorescence, hitherto undescribed. In conclusion, fluorescence, besides being absent in a large proportion of human subjects, has not been observed on the tongues of local herbivora (live sheep, or cattle tongues examined within half an hour of slaughter), cats, and fowls.

Acknowledgment is made to the Director of Medical Services, Bechuanaland Protectorate, for permission to record the above findings.—I am, etc.,

Lobatsi, Bechuanaland Protectorate. BERNARD T. SQUIRES.

REFERENCES

1 *Lancet*, 1928, 1, 281.
2 *British Medical Journal*, 1951, 1, 117.
3 *S. Afr. med. J.*, 1953, 27, 759.

Stellate Ganglion Block

SIR,—I had hoped the correspondence on stellate ganglion block would teach us more than it has done and would evoke a controversy, if not a scientific inquiry or assessment by a leading medical authority. Can it be that most general practitioners have fought shy of this subject, or medical authority frowns upon the almost inevitably haphazard observations produced so far, and has hence ignored them?

My own experience is limited to some 44 attempts, with little or no opportunity for accurate scientific assessment of results but sufficiently encouraging none the less. Like Mr. N. N. Iovetz-Tereshchenko (*Journal*, October 9, p. 870), I have found Horner's syndrome no indication of success or failure, but have observed a momentary hippus-like action upon the ipsolateral pupil. Anyone treating these patients prior to the inspiration of Leriche's paper[1] felt helpless and dissatisfied with orthodox treatment. It was encouraging to practise a method whereby the chances of reducing disability were considerable. Cerebral thrombosis and embolus are common, and this new treatment surely warrants investigation. What is being done?—I am, etc.,

London, W.8. JAMES RANDALL.

REFERENCE

[1] *Presse méd.*, 1934, **42**, 849.

Aetiology of Heart Disease

SIR,—Professor Melville Arnott in his Abernethian lecture (*Journal*, October 16, p. 887) appears to be impressed with the evidence supporting the theory of a high blood cholesterol and physical inactivity as causes of ischaemic heart disease, but he rejects the psychological theory and even considers the evidence adduced in its favour as absurd. When we examine the evidence for the former theory, however, there are several gaps and unanswered questions, while the author's treatment of the evidence in favour of the psychological theory would not be acceptable to most psychiatric opinion.

First, what were the habits of the private patients who consulted Osler and Mackenzie, who confessed to having seen very little coronary disease? Contemporary accounts of the dietetic habits of the well-to-do—such as that of General Haldane,[1] who was a guest of the Royal College of Physicians of Edinburgh at a dinner in 1881—show that they frequently ate their way through meals of many rich courses. Is it possible that the practice of eminent physicians in this era was drawn from a section of the well-to-do who were unusually abstemious and active?

The second question concerns the incidence of coronary thrombosis in the medical profession. The investigation of Morris *et al.*[2] showed that, where the incidence of coronary disease was tabulated according to occupational classification, the rate was twice as high in general practitioners as in the other groups. Again, although the authors admitted that the numbers were small, public officials, such as M.O.H.s, showed a much lower incidence.

How can these findings be interpreted in the light of the theory of physical inactivity and a diet rich in fat? General practice can hardly be called a sedentary occupation, whereas the public official has a definitely sedentary occupation akin to that of a business executive. Nowadays we do not associate medical practitioners in general with generous rich diets, and the nature of general practice is conducive to a rather frugal diet.

Then we come to bus drivers, who show a higher incidence of ischaemic disease than conductors. It is likely that neither enjoy a fat-rich diet, and, whereas the conductor is active and the driver is sedentary, the latter is exposed to psychological stress on account of his personal responsibility for the safety of the passengers. We should need to know if this stress is qualitatively different from that of the conductor responsible for the conduct of the passengers and the collection of fares.

Now to consider the question of emotional stress. Is Professor Arnott correct in assuming that the life of a physician in Birmingham is less stressful than that of a peasant in the Yangtse valley or a tribesman of equatorial Africa? This interpretation is unacceptable in the light of our modern knowledge of personality structure. The hazards of disasters such as floods and war are tolerable because the individual shares them with his group. The taboo and sanction of primitive belief mentioned by Professor Arnott may even be a source of emotional security for the tribesman. It is where personal guilt and conflict are involved that breakdown occurs, and we should not have expected breakdown in the Norwegian population during the German occupation. Thus the Norwegian example does not constitute a valid argument against the theory that emotional stress of a kind will cause ischaemic heart disease.

In view of the progress which we have made in the understanding of emotional security and the creation of an environment in which basic emotional needs are met, it is surely undesirable to reject the psychosomatic concept in so final a way as does Professor Arnott. Admittedly he emphasizes that there are many factors with which he has not dealt, but to the superficial or the non-medical reader, such as the journalist, his paper appears to give the final answer on this question. There remains much which requires further study, and one might hope that no premature attempt will be made in health education—a term which is preferable to "propaganda"—in this field until we have answers to these questions.—I am, etc.,

Bexley, Kent. A. J. DALZELL-WARD.

REFERENCES

[1] *A Soldier's Saga*, 1948. Constable.
[2] *British Medical Journal*, 1952, **1**, 503.

SIR,—In the *Journal* of October 16 (p. 887) I read with interest Professor W. Melville Arnott's paper entitled "The Changing Aetiology of Heart Disease." To a general practitioner, his classification of causes is practical and simple to understand; it is most informative. However, I am principally concerned with his observations on rheumatism and rheumatic heart disease. He draws attention to the gradual disappearance of the latter and ascribes the reason to the injection of penicillin and sulphonamides in streptococcal throats. I am in full agreement with this conclusion. In this area for the last ten years or more, all streptococcal throat infections have been treated in like manner. The treatment has been carried out in the patients' own homes by Jubilee nurses working under me. The immediate results have been dramatic. I have noted the long-term results to be the striking fall in the occurrence of rheumatic heart conditions.

About a year ago, while listening to a paper on juvenile rheumatism in the Academy of Medicine, Dublin, I mentioned to Dr. R. Steen, National Children's Hospital, Dublin, my experience of the gradual diminution of rheumatic heart disease and rheumatism in my district. I told him I attributed this fact to the treatment of streptococcal throats (the invasive stage of rheumatism, I presume, in some cases at least) by antibiotics and sulphonamides. I am interested to know that Professor Melville Arnott has had a similar experience. It would be a great triumph for medicine to abolish another crippling cause of invalidism in the younger generation.—I am, etc.,

Dalkey, Co. Dublin. JAMES I. ENRIGHT.

Operator and Anaesthetist

SIR,—I believe it is not unusual in dental practice for the dental practitioner to act both as operator and as anaesthetist, perhaps with the assistance of the dental nurse, who may continue the administration of nitrous oxide with or without air or oxygen after the dentist has completed the induction. In the case where thiopentone is being used as the anaesthetic agent, either solely or supplementarily, I have myself expressed the opinion[1] that in dental practice "thiopentone should never be given unless a second medical practitioner is present"—that is, of course, in addition to the dental practitioner who is to perform the operation. Dr. Victor Goldman[2] is even more categorical: "No anaesthetic should ever be administered for dental or other surgical procedures without a second qualified person being present except in the case of a sudden emergency." He makes it clear that by "qualified person" he means "medically or dentally qualified," not a nurse.

These opinions are now confirmed by a legal authority, Mr. William Mair, who is the solicitor to the Medical and Dental

Defence Union of Scotland, and who states[3]: "On no account should a practitioner endeavour to administer an anaesthetic whilst acting as operator also. . . . In my opinion, too great a risk was undertaken [in a recent case where the patient died during such a proceeding] in trying to act as operator and anaesthetist at one and the same time. The same observations apply to dental practice, and it is a sound, though not always a practicable rule, where the anaesthetic is being administered by a dental surgeon or his assistant, that the patient's doctor should have issued a prior certificate of the patient's fitness to receive the anaesthetic. Two instances have happened quite recently of the fatal collapse of a patient where such a precaution had not been taken . . . and in one case the presiding judge stressed the necessity for such a precaution."

In view of these opinions it seems likely that should an untoward event occur in a case where the dental surgeon acted as operator after himself administering the anaesthetic (and this presumably includes nitrous oxide as well as any other general anaesthetic agent), and the patient subsequently brings an action against him, he might have some difficulty in the absence of some good justification of his action—for example, in view of his experience of administering anaesthetics and in view of the great urgency of the operation and no other medical practitioner being available—in escaping liability. In view of the great importance of this matter I feel justified in claiming the hospitality of your columns in order to bring it to the notice of your readers.—I am, etc.,

London, W.1. R. BLAIR GOULD.

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[2] *Med. ill. (Lond.)*, 1954, **8**, 474.
[3] *Anaesthesia*, 1954, **9**, 248.

Death Due to Chloramphenicol

SIR,—There seems to be a widespread belief that chloramphenicol is a safe drug so long as it is not given in excessive dosage or for a prolonged period. Consequently it is still being prescribed for quite minor infections, where the physician, if he were aware of the risk, would presumably choose a less dangerous treatment. That even modest amounts of chloramphenicol may sometimes be lethal was brought home by a recent case.

A girl of 4 years had an attack of bronchitis with asthma for which she received 1 g. chloramphenicol daily for four days. Six months later she developed a sore throat, which was treated with a further course of chloramphenicol 1 g. daily for four days. Three days after completing this course a purpuric rash appeared and in spite of blood transfusion she died two weeks later. An aplastic anaemia (confirmed at necropsy) had followed the second of two courses of 4 g. chloramphenicol.

There is also a general impression that chloramphenicol is an effective treatment for whooping-cough, although controlled trials have shown that treatment is without effect on the clinical course of the illness when it is started after the eighth day of symptoms, and that even when treatment is started in the first week its effect is only slight.[1 2] May I put forward a plea that chloramphenicol be prescribed only after careful thought has ensured that no safer treatment is applicable, and that the small but definite risk unavoidable with the use of this drug is really justifiable?—I am, etc.,

Cambridge. DOUGLAS GAIRDNER.

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[1] *British Medical Journal*, 1953, **2**, 769.
[2] Morris, D., and Cockburn, W. C. (1954). *Lancet*, **2**, 724.

Accidental Carbon Monoxide Poisoning

SIR,—With reference to the article entitled "The Danger of Accidental Carbon Monoxide Poisoning," published under the name of Dr. Keith Simpson (*Journal*, October 2, p. 774), and his comment that "the apparent unconcern with which the gas authorities take this alarming toll of life [gas fatalities] is astonishing," I would wish to add comment.

The radio and the popular press are regularly commenting upon the frequent carelessness of the medical profession and hospitals in handling dangerous drugs. Through carelessness on the part of the medical profession in the first instance, even children are able to abscond with their highly dangerous concoctions. Similar comment might be made on the recent press announcements regarding the liberal dispensation of drugs to help patients suffering from insomnia. Would Dr. Simpson consider it fair comment for me to write in *Gas Times*: "The apparent unconcern with which the medical fraternity view their responsibility for handling dangerous drugs and avoiding them getting into the wrong hands is astonishing"?

Presumably the medical authorities do not accept departure from their security procedure lightly—and, indeed, neither do the gas boards. There is, of course, one common stumbling-block to both authorities, and that is that, to the potential suicide, gas and sleeping pills are equally attractive, whilst carelessness in the use of both gas and dangerous drugs can lead to tragedy.—I am, etc.,

Watford. W. F. COXON, Editor, *Gas Times*.

SIR,—With reference to the article by Dr. Keith Simpson on "The Dangers of Accidental Carbon Monoxide Poisoning" (*Journal*, October 2, p. 774), I am wondering how many non-fatal cases of poisoning are occurring. The practice of heating bedrooms by means of portable paraffin heaters is common and is taken to excess by Americans living in this country. I have often wondered if the carbon monoxide given out by these heaters causes a certain amount of anaemia and ill-health. The gas cooker, which practically never has provision for removing fumes, may also be a source of slow poison to the unsuspecting housewife.

I should be most interested to know if any investigations have been carried out for the kind of case I have outlined.—I am, etc.,

Godmanchester, Hunts. JOHN HYNES.

West London Hospital Medical School

SIR,—The letter from some past students of the West London Hospital Medical School (*Journal*, October 16, p. 930) was very welcome in helping to clear the confusion concerning this school. The achievements of those who signed this letter are indeed a sufficient tribute to the school that trained them.

I should like to add one observation, as yet another past student now working in the hospital laboratories, in protest against the view that their teaching strength is inadequate. The teaching staff is not large; but it is unfailingly courteous, witty, and often inspiring. The laboratories are modern and well equipped, and the museum contains a number of much-disliked "examination specimens." There is a continuous research tradition both in the general laboratories and under the aegis of the Dan Mason Research Foundation of the medical school; and notable contributions have been made in the fields of renal function assessment, basal metabolism, neurophysiology, and disorders of blood coagulation by members of the staff. Of all the students qualifying from this school, more than one-tenth have been sufficiently interested to have sought further training in laboratories.

Those of us who have been trained in the West London laboratories regard them with great affection, and know that when we bring problems to them we will always receive a friendly welcome and a sound solution.—I am, etc.,

London, W.6. I. J. L. GOLDBERG.

SIR,—I wish to add my support to those who have recently written to you (*Journal*, October 16, p. 930) on the subject of the future of the West London Hospital Medical School. I agree with them that the small size of this school, far from being a drawback, was, to all of us who trained there, a very great advantage. For the very reason that it was small we obtained there far more individual experience and tuition than would have been possible in a larger school. Surely this less formal type of training is more likely to produce doctors with the practical clinical experience so

necessary in the problems of everyday practice? If the authorities destroy this school they will deprive the profession and the community of a training centre which could render an invaluable service at a time when other London medical schools are not only overcrowded but are being forced to refuse admission to a large proportion of their applicants.—I am, etc.,

London, N.W.3. PATRICIA D. GRAEME.

St. John's Hospital, Lewisham

SIR,—Mr. Charles Beney (*Journal*, October 16, p. 931), on the subject of St. John's Hospital, Lewisham, refers to certain characteristics of the Park Hospital which might make it unsuitable as a site for a surgical unit. This raises the question of the future of hospitals which formerly maintained large numbers of beds available to deal with outbreaks of infectious disease. Far fewer infectious cases are being admitted than before the war, and whole wards, and even whole blocks of wards, have been closed. In the case of the Park Hospital, these wards had generous spacing for beds and ample side ward accommodation. In one block an operating theatre was available.

At Lewisham Hospital—the largest wholly general hospital in the South-East Metropolitan Region—extensive bomb damage has made the surgical bed situation a real problem. This problem was particularly acute in the throat and ear department, where the number of out-patients seen has greatly increased recently, and was last year well over 4,000. The number of beds required and the facilities for operating theatre sessions and specialized nursing were not available. A patient who had had a laryngectomy or major labyrinthine surgery had to be nursed in a ward which might also have general surgical, genito-urinary, gynaecological, ophthalmic, and orthopaedic cases. For these reasons it was decided to establish an in-patient unit, consisting of one male, one female, and one children's ward at the Park Hospital. The construction of the buildings made it possible, with insignificant alterations, to arrange for each ward to have an examination room in which patients, whether in bed or up, can properly be examined and treated under bright illumination. The theatre has large, separate anaesthetic and recovery rooms.

The gardens and grounds of the Park Hospital have long been well known for their spaciousness, and this self-contained unit is at one end of these grounds. This is one example of the use to which the buildings formerly used for infectious diseases can be put, with little capital expenditure. The regional neurosurgical and thoracic surgical units at the Brook Hospital, Woolwich, are others on a much larger scale. All in all, therefore, the possibility of establishing surgical units in hospitals such as the above should not lightly be dismissed.—I am, etc.,

London, W.1. KENNETH WILSON.

Encephalitis after Yellow Fever Vaccination

SIR,—I was interested to read Dr. J. Hewgill Smith's account of encephalitis in an infant after vaccination with 17 D yellow fever virus (*Journal*, October 9, p. 852), as I have recently had such a case under my care. The patient was a boy admitted to hospital on September 9, 1954, aged 8 weeks. He returned from Lagos on September 17 having been given a yellow fever vaccination (17 D virus) on September 11.

He had been listless for five days, had a slight convulsion the evening before admission and two severe ones the day of admission to hospital. On clinical examination the child was drowsy and his rectal temperature was 101° F. (38.3° C.). The anterior fontanelle was normal and no other abnormality was found. *Investigations.*—C.S.F. from lumbar punctures (October 1) showed 133 leucocytes per c.mm. (mostly lymphocytes), R.B.C. 55 per c.mm., protein 140 mg.%, sugar 55 mg.%, culture sterile; October 2, chlorides 700 mg.%, sugar 58 mg.%; W.B.C. 13,500 per c.mm. (polymorphs 42%, lymphocytes 54%, hyalines 4%). Throat swab grew *Staphylococcus aureus*, coliform bacilli, and *Streptococcus viridans*. Chest *x*-ray N.A.D. Urine no albumin, nil abnormal in the deposit, and no growth on culture.

The main treatment given was aureomycin 50 mg. orally six-hourly and chloral hydrate grains 2 (0.13 g.) six-hourly. The baby's temperature fell to normal on October 3 and remained so until discharge on October 12. He ceased taking aureomycin on October 8. On October 4 he appeared less drowsy and was quite well on discharge from hospital. He will be seen again in the out-patients department.—I am, etc.,

Bexhill-on-Sea, Sussex. LESLIE G. SCOTT.

Prevention of Colds

SIR,—It was refreshing to read the account of the experiment for the prevention of colds in offices made by Drs. O. M. Lidwell and R. E. O. Williams (*Journal*, October 23, p. 959) with hexylresorcinol, and they are to be congratulated for sending it for publication. So much thought—and the subject deserves much thought—for the prevention of colds seems to be based on the same false premises as this experiment. Is it not as nearly proved as is possible in a question of this kind that the epidemic spread of colds is due to the balloon of spray emitted and projected by speech or coughing from the infected person to the uninfected victim, and not by infective agents vaguely floating about in the air? A more logical, and probably a more profitable, method would be to divide a large desk at which, say, three clerks are at work on each side by a glass screen to separate those who face one another, and smaller screens arranged at right angles to the first to separate those who sit side by side. It is not unusual for an influenza epidemic to result in an absentee list of 20% or more.—I am, etc.,

Bunbury, Cheshire. HERBERT TERRY.

SIR,—As Dr. O. M. Lidwell and Dr. R. E. O. Williams refer directly to me in their report (*Journal*, October 23, p. 959), perhaps you will allow me to comment briefly at this stage. First, the statement is made that there was "no evidence of any effect on the attack rate for the common cold and other similar affections, nor on the absence rate" by the diffusion of hexylresorcinol "at a temperature of about 116° C." With this conclusion I entirely agree. It has been found that the optimum temperature for the release of this agent as an effective aerosol is 126° C., and it is understandable therefore that, as stated, "air samples taken in October, 1952, showed barely detectable amounts of hexylresorcinol present in the air," and that no significant difference was observed as between test rooms and control.

Secondly, by own observations,[1] continued over five years and related to the sickness experience of many hundreds of persons, confirmed the laboratory work of MacKay,[2] who recorded the remarkable bactericidal power of hexylresorcinol as a continuous-flow aerosol diffused at the optimum temperature of 126° C. The issue would appear to lie between MacKay and Lidwell and Williams. They cannot both be right.—I am, etc.,

Killiney, Eire. CHARLES DICKSON.

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[1] *Irish J. med. Sci.*, 1953, 6s, 337.
[2] *J. Hyg. (Lond.)*, 1952, 50, 82.

Pilonidal Sinus

SIR,—Dr. R. H. Jones in his letter (*Journal*, October 23, p. 990) following your leading article on pilonidal sinus (*Journal*, September 18, p. 694) describes the post-operative care—personal hygiene and a comfortable cushion when driving Army vehicles—which he impressed on his patients. I likewise treated a few men for this condition in the Suez Canal zone when serving in the medical branch of the R.A.F. In at least two of these it was possible to trace attached hairs growing upwards in the natal cleft and entering the pilonidal abscess. After operation in one patient the hairs of the surrounding skin began to grow into the recently healed area, causing excoriation of its thin surface. This

was stopped by shaving of the natal cleft, a step which had already been carried out pre-operatively three weeks before.

On this and other instances I feel that routine shaving of the natal cleft in addition to personal hygiene is an important measure for preventing recurrence of pilonidal sinus, a condition which so often occurs in individuals with particularly wiry hair. It will be of more importance in hot climates than temperate, as a raised skin temperature favours a more rapid growth of hair. Wide excision of a pilonidal sinus as practised by many surgeons may prevent recurrence by the removal of a larger area of hair-bearing skin. It also has the effect of making the upper part of the natal cleft wider and more shallow so that the hairs of the neighbouring skin which tend to grow parallel to the surface are less likely to "dig in." On this reasoning, the conservative excision described by Dr. Jones, although it gives a shorter stay in hospital, is likely to have a higher recurrence rate in the absence of post-operative routine shaving. The action of continued rubbing of a sweaty and hairy natal cleft when driving vehicles is undoubtedly contributory to the formation of a "pilonidal sinus" or "jeep seat," but its effect should be reduced by shaving. This, with personal hygiene, should prove a better deterrent than providing a comfortable cushion which in hot climates will increase the retention of sweat in the natal cleft. Since the acceptance of pilonidal sinus as an acquired condition[1,2] the importance of local hygiene has been stressed. I do not think the logical procedure of routine shaving of the natal cleft with its increased ease in personal hygiene has previously been emphasized.—I am, etc.,

London, N.W.1. MILO KEYNES.

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2 Hueston, J. T. (1953). *Brit. J. Surg.*, 41, 307.

Late Effects of Syphilis

SIR,—The annotation on the late effects of syphilis (*Journal*, October 16, p. 923) is on the whole misleading. The impression given is that late syphilis should have diminished in incidence in parallel with early syphilis. The manifestations of late syphilis follow early syphilis usually not less than ten years later, often much later than this, and quite often up to forty years later. Many cases of late syphilis following early syphilis in the first world war are still appearing. Since the incidence of early syphilis began to fall after 1946, there cannot be expected a fall in late syphilis until 1956, and even then it cannot be expected to fall at the same rate as early syphilis, because the incubation period varies from ten to forty years. It is true that syphilis in the armed Forces was treated mainly by erstwhile skilled civilian specialists, but also in civilians were many cases similarly treated. The real factor in success in treatment here was the absolute control over defaulting in the armed Forces, as opposed to the absence of control in civilians. Many civilians suffered from syphilis and many defaulted from treatment, and of these there will be the usual proportion of cases of late syphilis later.

The following statement in the annotation, that "interstitial keratitis, for example, is easily prevented but almost impossible to cure," is a depressing picture and misleading. If microscopical cure is meant, then there is some truth in this, but as far as clinical cure is concerned, and this is what interests the sufferer, it is not true. The recent local treatment with cortisone combined with intensive general treatment has certainly resulted in clinical cures in a large proportion of cases.—I am, etc.,

Norwich. H. L. ROGERSON.

Appendicectomy in Chronic Appendicitis

SIR,—As a doctor trained in pure science before I had any idea of taking up medicine, I am amazed—indeed appalled—at the way in which three of your correspondents, Drs. Ian G. Wickes and E. K. Westlake (*Journal*, October 9, p. 869) and Mr. D. P. van Meurs (*Journal*, October 23, p. 991, presume to tell the authors of "Justification for Appendicectomy in Chronic Appendicitis" (*Journal*, September 25, p. 736) that they are wrong. Almost the first thing we were taught at Cambridge was the virtual impossibility of proving a negative. As was stated at the Comet inquiry recently, "it is not impossible, but it is exceedingly difficult." Yet here are three doctors, who seem to pride themselves on their scientific outlook, denying results on patients whom they had not even seen. It is true that they are in the company of many pharmacologists, but that does not make them right or their attitude scientific.

The best and perhaps the only real way to test the reality of some "cures" is to live among the patients who have been "cured" and watch them, their families, and associates for years before and afterwards. By this test I can unhesitatingly confirm the general validity of the conclusions of Messrs. McLennan and Watt. Done in the right circumstances, there is no operation which gives such general satisfaction as that for chronic appendicitis; but I would add that in many of these cases pain in the right iliac fossa is not a presenting symptom or even present at all, and certainly many of them are quite unaware that their appendix has anything to do with their trouble. The probability that there are some people who do have a sort of neurosis about their appendix, as your correspondents suggest, is no ground for denying the reality of the successes recorded in the article. It simply means that your correspondents have not been happy in deciding on which cases should have operation and which be left alone.

It is easy to say that those who believe in the efficacy of operation are deluding themselves, but in my experience these patients are their own controls. One has only to note how so many of them haunt one's surgery for years, while one tries on them every therapeutic measure available without success, and then note how after operation they cease to trouble any more, to be convinced that it is not one's personality or psychological influence that has wrought the change but the operation itself. If, however, the patient is treated in the impersonal, semi-contemptuous, sausage-machine-like way which the "chronic appendix" sometimes suffers it is quite possible for a psychological trauma to be inflicted which replaces the physical irritant that has been removed, thereby bringing the operation into the disrepute in which your correspondents glory. But, properly performed with sympathy and care, the operation is eminently satisfactory in quite 90% of cases, and only those blinded by prejudice could fail to observe it.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

SIR,—I feel I must support the paper by Mr. Iain McLennan and Mr. J. Kennedy Watt (*Journal*, September 25, p. 736) entitled "Justification for Appendicectomy in Chronic Appendicitis." Some years ago Mr. S. K. Kay and I entertained some doubts as to the existence of the clinical entity of chronic appendicitis. A study of the literature only increased our confusion because of the divergent and conflicting views expressed. This led us to conduct a survey of approximately 130 consecutive cases of chronic appendicitis for which appendicectomy had been performed in Law Hospital a few years previously. The basis of the survey was similar to that of Mr. McLennan and Mr. Watt, and we were extremely surprised to find a nearly 80% "cure rate." The sincere expressions of gratitude by many of the patients were even more marked. No patient was made worse.

Several general practitioners in the area were asked for their views as to the benefits of appendicectomy on their patients. All expressed satisfaction with the results, and one went so far as to say: "It seems to me that to deny the presence of chronic appendicitis is in itself psychological." Like many others, however, we were unable to find any relationship between the clinical, operative, and pathological findings. The relief of symptoms following appendicectomy may not prove that chronic appendicitis is a clinical entity, as pointed out by the letters of Drs. Ian G. Wickes and E. K. Westlake (*Journal*, October 9, p. 869) and Mr. D. P. van Meurs (*Journal*, October 23, p. 991), but we have at least attained our main aim as doctors—the cure of

our patients. The doubters seem very pleased with themselves for having resisted the temptation to remove what may be a normal-looking appendix and yet are happy to leave the patient with his pain, the relatives with their doubts, and the general practitioner with an unhappy patient to haunt his surgery.—I am, etc.,

Carluke, Lanarkshire. J. A. MACFARLANE.

Idiopathic Hypochromic Anaemia in Males

SIR,—Dr. J. W. B. Forshaw's article on idiopathic hypochromic anaemia in males (*Journal*, October 16, p. 908) was most interesting. This condition is extremely rare but undoubtedly exists, and I have recently seen a young man suffering from the disease. The patient, aged 17, visited his doctor for another purpose and was noted to be very pale. When reporting to the laboratory for a blood count, he stated that he felt perfectly well and was doing a full day's work in a market garden. He had well-marked koilonychia, and blood examination showed : haemoglobin 47% (7 g. per 100 ml.), R.B.C.s 4.9 million, colour index 0.5, M.C.H. 14 $\gamma\gamma$, M.C.H.C. 22%. In the stained film the red cells showed considerable anisocytosis, microcytosis, and hypochromia. There was no evidence of blood loss or haemolytic anaemia. He was put on full doses of iron by mouth, and in seven weeks the haemoglobin had risen to 103% (15.2 g. per 100 ml.) and remained at this level for over twelve months without treatment. It is essential, in these cases, to exclude blood loss and congenital haemolytic anaemia.—I am, etc.,

Haywards Heath. R. W. P. JOHNSON.

Agammaglobulinaemia

SIR,—With reference to your annotation (*Journal*, October 23, p. 976) at least three cases of agammaglobulinaemia in adults appear to have been recognized before the case reported by Sanford, Favour, and Tribeman.[1] Sturgis reported what was believed to be the second case in an adult during the discussion following Janeway, Apt, and Gitlin's paper.[2] This patient was a man aged 36, who had had repeated respiratory and other infections. Also Van Dommelen and Schulte,[3] in an article on the clinical value of the investigation of serum proteins by filter-paper electrophoresis, mention a patient who had been suffering for years from an obscure disease resembling sepsis and who was found to have a deficiency in gamma globulin. She was a woman aged 50.[4]

As to diagnosis, the qualitative filter-paper electrophoresis technique is of such beautiful simplicity (it can, if necessary, be done on a drop of serum obtained by finger prick) that there appears to be little advantage in arriving at the diagnosis by more roundabout methods such as investigating the isohaemagglutinins as recommended by you. Quantitative electrophoresis is unnecessary, since the concentration of gamma globulin in these cases is always less than the minimum detectable by the method. The vast majority of cases of multiple sepsis have, of course, normal concentrations of gamma globulin in their sera.—I am, etc.,

Shrewsbury. GREGOR H. GRANT.

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3 *Pharm. Weekbl.*, 1953, **88**, 669.
4 van Dommelen, C. K. V. Personal communication.

Retrolental Fibroplasia

SIR,—Your leading article on retrolental fibroplasia (*Journal*, September 18, p. 692) prompts me to record the paucity of cases amongst the African Bantu (like the Negro in America). I have had occasion to examine numerous premature African babies and not once did I observe even the earliest signs of retrolental fibroplasia. These babies do very occasionally receive minimal amounts of oxygen, which helps to support the hyperoxia theory.

The number of premature infants amongst the European population in Rhodesia is small and one has to rely mainly on the literature and case reports to watch developments. A point that has occurred to me from the study of case reports is the numerous recoveries and improvement in suspected cases of retrolental fibroplasia by the injection of procaine benzyl penicillin intramuscularly. Is this merely a coincidence or does it favour an infective theory ? Some conclude that the penicillin clears an incipient or subclinical bronchopneumonia, thereby assisting oxygenation and proper pulmonary ventilation—this precludes the development of the anoxic state.—I am, etc.,

Bulawayo. IAN SACKS.

New Blood-transfusion Sets

SIR,—I wish heartily to endorse the feelings of the two house-surgeons for their paradoxical " new-style " giving sets for blood transfusions (*Journal*, October 23, p. 994). I have felt on many occasions that an impaled nurse on the end of the air entry needle would be the more likely result than successful entry into the stubborn bottle, only to find, having gained the elusive admittance, that a piece of rubber had blocked the needle. Leaks can be coped with by devious means, but frequently, having left the ward, one is recalled in panic by the message that the drip chamber has suddenly filled and the drip has stopped. Short of using another set there seems no easy method of emptying the chamber as there was with the older pattern of set. During the more serious business of rehydrating ill infants and neonates, and rapidly transfusing blood to collapsed patients, precious time is obviously lost by these defects. Making the sets " international " is one thing, but could they not be more mechanically sound first ?—I am, etc.,

West Bromwich. B. E. NOBLE.

Cancer Risk

SIR,—In view of the correspondence on naphthylamine, etc., as a possible cause of cancer of the urinary bladder, I might just mention that one of the very few persons I have known who died of cancer of the urinary bladder was an elderly man devoted to his occupation as pharmaceutical chemist—sometimes at a hospital and sometimes working on his own account. He would take an active interest in everything that went on under his supervision, and I cannot help thinking that his occupation, necessitating the handling of all kinds of chemical products, might possibly have had something to do with his death from cancer of the urinary bladder.—I am, etc.,

London, N.W.1. F. PARKES WEBER.

Family Planning Association

SIR,—Although the Family Planning Association was formed in 1939, there are many medical practitioners who do not know of its existence or of the facilities it offers. There are at present approximately 170 clinics in the country and the number is increasing rapidly ; some branches have more than one clinic. Although each branch of the association is autonomous, and is organized to meet the special needs of the areas, there is a constitution common to all.

The following are some points as to how the clinics function. Every clinic gives practical advice on contraception. Some also give advice on sub-fertility. Every patient is seen by a doctor attached to the clinic and who has had special training. Although these clinics are open to all married women, the association welcomes especially patients sent by their family doctor, who is notified after the interview. The association is not under the National Health Service, and patients are charged a small fee, but special arrangements are made for the necessitous.

Further information can be obtained from Headquarters, 64, Sloane Street, London, S.W.1.—I am, etc.,

HORDER,

London, W.1. President, Family Planning Association.

Obituary

J. H. L. CUMPSTON, C.M.G., M.D., D.P.H.

Dr. J. H. L. Cumpston, who was Director-General of Health for the Commonwealth of Australia for nearly a quarter of a century, died on October 9 at the age of 74.

John Howard Lidgett Cumpston was born at Melbourne, on June 19, 1880. From Wesley College, Melbourne, he entered Queen's College, Melbourne University, as a medical student and graduated M.B. in 1902, taking the B.S. degree in the following year. He proceeded to the M.D. in 1907. After graduation he held house appointments at Melbourne Hospital and as assistant medical officer at the Parkside Asylum, Adelaide, before coming to London as a member of the staff of the Western Hospital under the old Metropolitan Asylums Board in 1906, the year in which he obtained the D.P.H. of the English Royal Colleges. Two years later he returned to Australia to assume the duties of his first public health appointment as medical officer of health for Western Australia, a post he relinquished in 1911 to become chief quarantine officer for Queensland.

In 1913 Cumpston was appointed director of quarantine for the Commonwealth, and in 1922 he became, in addition, Director-General of Health. He filled both posts with great distinction until he retired in 1945. The responsibility he had to shoulder in this dual capacity was no light one, for during his tenure of office Australia was welcoming immigrants in large numbers. In addition, the country's immense coast-line makes the work of a quarantine officer exceptionally difficult. For his services Cumpston was appointed C.M.G. in the New Year Honours of 1929.

On the occasion of the Centenary celebrations of the British Medical Association in 1932 Cumpston returned to London to serve as a vice-president of the Section of Public Health. In 1937 he was appointed chairman of the National Health and Medical Research Council in Australia, and in 1942, during the last war, he did good service as director-general of the Emergency Civil Practitioner Service. Four years ago he visited Java, Malaya, and Siam on behalf of the United Nations International Children's Emergency Fund.

Cumpston undertook a good deal of historical research on health subjects and published books on the history of smallpox, plague, and intestinal infections in Australia. Other books from his pen include *The Practice of Maritime Quarantine* and *Public Health in Australia*. For recreation he turned to fishing, particularly sea-fishing, and in his younger days enjoyed the rather unusual pastime of bookbinding. He married Miss Gladys M. Walpole, daughter of Dr. G. A. Walpole, and had three sons and four daughters.

Sir FRANK CONNOR, D.S.O., F.R.C.S.

Major B. J. BOUCHÉ, I.M.D. (ret.), writes from Queensland:

It was with regret I read the obituary of Sir Frank Connor in your issue of August 21 (p. 472). Having been his assistant in the *x*-ray department of No. 8 Indian General Hospital at Amara in Mesopotamia in 1916 during the first world war, I can speak with first-hand knowledge and experience of an officer whom work could never tire, and who had the enthusiasm of a young graduate and a remarkable memory for facts, figures, faces, and names. He showed the essence of politeness to everybody, seldom permitted himself to get ruffled, and never refused to do anyone a good turn if he could. In short, he was just what a cultured man ought to be. If I remember aright, it was to Sir Frank, then just Major Connor, that the lion's share of the credit for the invention of the telephone probe was due, a useful appliance in war surgery which Connor tirelessly demonstrated to young officers in the marquee serving for both *x*-ray department and operating theatre. In the great heat of Mesopotamia our radiological work was done mostly between 6 p.m. and midnight, but when boats full of sick and wounded requiring immediate attention arrived in the River Tigris hours later Connor was first there to render succour. He filled the appointments of registrar and second-in-command, radiologist, surgeon to the hospital, and consulting surgeon to the Forces. They were not easy days. Those of us still living will remember the state of affairs which necessitated the Vincent–Bingley Commission. Energy, enthusiasm, ethics, and excellence were O'Connor's overwhelming possessions.

Dr. WILLIAM BELL, formerly physician to St. Luke's Hospital, Bradford, died on October 2 at his home at Dufton, near Appleby, where he had lived in retirement for some years. William Bell, who was born on December 17, 1876, had a distinguished student career at Edinburgh University, where he graduated M.B., Ch.B., with honours, in 1898. He proceeded to the M.D. in 1912, receiving a commendation for his thesis. After graduation he was for a time demonstrator of physiology in the university, and later he held a resident post at the Cumberland Infirmary, Carlisle. Subsequently he volunteered as a civil surgeon in the South African war and was medical officer in charge of a hospital in Cape Colony. For his services he received the Queen's medal and clasp. On his return he settled in a country general practice at Skelmanthorpe, near Huddersfield, and became a prominent practitioner in the district, being president of the Huddersfield Medical Society for a term. He left Skelmanthorpe in 1919 to go to Edinburgh for postgraduate work in medicine, and in 1920 he was elected a Member of the Royal College of Physicians of Edinburgh, becoming a Fellow seven years later. When he moved to Bradford in 1921 he was immediately appointed physician to St. Luke's Hospital, which was one of the first municipal general hospitals to be established. He continued to practise in Bradford until he retired in 1946 on reaching the age of 70. He was chairman of the Bradford Division of the British Medical Association in 1935–6. In 1935 Dr. Bell bought a house, as a residence, in the village of Dufton among the fells of Westmorland. He continued to work at St. Luke's Hospital and remained on the active staff until the end of the last war, usually motoring home to Dufton at week-ends. He was interested in the country, country life, and farming, and was a dog fancier, and at Dufton was able to live the life he really desired. He was also keen on horses and riding, and for some time made his professional visits on horseback when in practice at Skelmanthorpe. At Bradford, also, he had interests apart from medicine. He was a founder member and, for a term, president of the Bradford Rotary Club and was a former president of Bradford St. Andrew Society. One of the early owners of a car, he became eventually an enthusiastic motorist and took a delight in driving a high-powered car at speed, thinking nothing of the 100-mile journey from Bradford to Dufton. William Bell was a man of ability, a keen observer, and a clear thinker, and he kept himself well informed by reading. He was a good and reliable friend and a pleasant travelling companion. His wife died at Bradford in 1925, and he is survived by his two sons, the elder, Robert D. Bell, being a major in the R.A.M.C.—W. W.-S.

I. D. C. writes: Those of us who were associated at St. Luke's Hospital, Bradford, with Bill Bell, as he was affectionately known to his residents, will regret the passing

of a physician whose long contribution to the development of that hospital and service to the community will well be remembered. Appointed as a consultant there in the early 'twenties, he delayed his retirement until after the last war, although suffering from a serious illness during his last year or two on the staff. He was a clinician of the older school and practised in general medicine, child health, and dermatology, a versatility which was developed in his earlier days in general practice. His sound clinical knowledge was augmented by a keen academic interest in his profession, and through his wide reading he kept abreast of the times, following closely the advancements in modern medicine even after his retirement. He was possessed of a splendid memory which enabled him to utilize the knowledge thus acquired to the full advantage of the patient. His readiness to help those who came for advice was greatly appreciated, particularly as it was so willingly and effectively given. A steady, deliberate approach to hospital work was a contrast to his joy of motoring at high speed to and from his home in Westmorland, the countryside he loved so much.

Medical Notes in Parliament

CLEAN FOOD BILL

The Food and Drugs Amendment Bill was subjected to close examination in the House of Commons on October 26 and 27. The proceedings in committee were mostly in charge of Dr. CHARLES HILL, Parliamentary Secretary to the Ministry of Food, with Mr. D. HEATHCOAT AMORY, now Minister of Food as well as of Agriculture, accepting substantially the role of observer.

On Clause 1 (Offences in connexion with preparation and sale of injurious foods and adulterated drugs) Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) supported an amendment moved by Mr. N. DODDS (Dartford, Lab.) to add a new subsection requiring that no person should abstract or direct the abstraction of any constituent of food so as to change the nature, substance, or quality of food intended for human consumption without notice of the alteration to the purchaser. Mr. DODDS said that such a provision appeared in the parent Act of 1938, and it was important that it should be included again. Dr. BROUGHTON urged the Minister to accept this and associated amendments which aimed at preventing wholesome food from losing the richness of its vitamins and minerals.

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) called attention to phrases in the Bill which he said he had never been able to define to his own satisfaction, phrases such as "the health of a person," and "the probable cumulative effect of articles of substantially the same composition on the health of a person consuming such articles in ordinary quantities." This led him to seek a definition of good health in the funeral oration of Pericles over the Athenian dead, which he adapted by the alteration of one word to read: "It is the state of moral, mental, and physical well-being which enables any man to face any crisis in life with the utmost facility and grace." He sought from the Ministry, if they could not give their views on what constituted good health, at least some indication of what was meant by "cumulative effects." Had they in mind the repeated use of lead sprays on fruit, for example, or the cumulative effect on a child of eating iced lollies? Dr. CHARLES HILL explained that section 2 in the 1938 Act had been found to be unworkable. But his main answer was that the approach in this Bill had been to distinguish between additions that were injurious and those that were not. There was an absolute prohibition on addition, subtraction, or processing that was injurious to health. Non-injurious additions were dealt with under other clauses, and what Mr. Dodds had in mind was achieved. The terms "health of a person" and the "probable cumulative effects" would be for the courts to decide, and they might reach speedier conclusions than doctors on the matter. He added in answer to complaints about the difficulties of legislating by reference to the principal Act that the Government intended to introduce a consolidation Bill at the earliest possible moment. The amendment was negatived.

Advertising Injurious Foods

Sir LESLIE PLUMMER (Deptford, Lab.) moved to omit subsection (6), which provides that in any proceedings relating to the advertising for sale of a food or drug injurious to health it should be a defence if it were proved that the advertisement was dealt with in the ordinary course of business. He argued that in the interests of pure food the defence should not be allowed. Most advertising agents were reputable and responsible, but there was a minority whose only interest was making money quickly. Mr. HEATHCOAT AMORY objected that the amendment would throw an unreasonable onus on the advertisers, whereas it should rest squarely on the manufacturers. Dr. EDITH SUMMERSKILL (Fulham, West, Lab.) pressed the amendment to a division. What they were anxious to do, she said, was to give the maximum protection to the consumer. Food technology had advanced to such an extent that this was necessary. Not only should the manufacturer face up to his responsibilities, but so should the advertiser. The arguments that had been used against the amendment were not relevant when the commodity was food. The amendment was rejected by 255 votes to 222.

On Clause 3 (Regulations as to composition of food, etc.), a Government amendment was agreed to, adding a new subsection (4) giving authority for the seizure of food not complying with the regulations. Dr. HILL gave an assurance that it was proposed to continue the work of the Food Standards Committee.

On Clause 4 (Powers of Ministers to obtain particulars of certain food ingredients), Dr. EDITH SUMMERSKILL moved two amendments, one to insert the words "or in any other way affects," and the other an additional subsection covering investigations carried out by manufacturers to determine "the cumulative effect on the health of a person consuming such substance in ordinary quantities." She said that her purpose was to strengthen the Minister's powers. In present-day circumstances the whole approach was exploratory. No one could be dogmatic about the effects of new drugs or adulterated foods. The effect might be injurious to health, or it might affect the individual in some other way, even causing changes in personality. To-day there were only two foods free from artificial ingredients—fish and wild fruits. The Minister should take the widest powers offered him. Mr. HEATHCOAT AMORY agreed, and the amendments were agreed to.

On Clause 6 (Regulations as to food hygiene) the Opposition pressed an amendment making it mandatory instead of permissive for the Ministers of Food and Health to make regulations for securing sanitary conditions and practices in connexion with the sale, preparation, and transport of food. The amendment was rejected by 228 votes to 213.

Three amendments moved by Dr. BROUGHTON were accepted by the Government. They required that the regulations relating to catering establishments should cover drainage, water supplies, and refuse disposal. Dr. STROSS secured the acceptance of an amendment insisting that every sanitary convenience in such premises should be supplied with water through a suitable flushing appliance.

Dr. EDITH SUMMERSKILL proposed that persons engaged in preparing, handling, wrapping, or delivering food should be medically examined and that sufferers from or carriers of infectious disease should be prohibited from engaging in such work. Dr. HILL said there was existing provision under the public health and infectious diseases regulations for preventing the spread of infection. When this Bill was passed it was proposed to make regulations providing that if a

person engaged in handling food became aware that he was suffering from one of a list of diseases (which could be extended) the medical officer of health was to be notified. That did not go the whole way that Dr. Summerskill wanted, but it did set going the compensation machinery. He did not pretend this was ideal, but the other proposal for medical examination of about 180,000 people engaged in catering establishments was a formidable prospect. If it was to be of value, the examination would have to be regular and repeated, and if it was to reveal a carrier it would have to be of a detailed bacteriological kind. The amendment was rejected by 231 votes to 208.

Dr. SUMMERSKILL had better fortune with an amendment requiring that regulations should cover the provision and use of wrapping materials in which food was sold or prepared for sale. She spoke of the use of newspapers bought by retailers from houses for the wrapping of food, and said that much of it came from rooms where there had been illness, perhaps chronic illness. Dr. HILL agreed that there was some doubt whether the clause gave sufficient power for this purpose without the amendment. The word "packaging" might prove too limited, and he accepted the principle of adding words to meet the problem of wrappings, but reserved the right to study the drafting—there was also the problem of plastic wrappings. Dr. SUMMERSKILL accepted this assurance, and the amendment was withdrawn.

Spitting Prohibited

Dr. SUMMERSKILL won her point in a subsequent discussion on the prohibition of spitting. She moved to insert in the clause a subsection requiring that the regulations should prohibit spitting on premises where food was sold, offered, exposed, stored, or prepared for sale, including any parts of the premises in which apparatus and utensils were cleansed. She insisted this time that the words she proposed must be incorporated in the Bill. Mr. SOMERVILLE HASTINGS (Barking, Lab.) sought to add a prohibition of smoking during the preparation or serving of food, which he said he had seen not only in catering establishments but also in hospital kitchens. Much stronger than aesthetic objections, he said, was the fact that it was difficult to smoke a pipe and impossible to smoke a cigarette to the end without being liable to get some saliva on the hands and the consequent danger of infecting the food. Dr. STROSS supported the amendment, and, while commenting on the undesirability of chewing-gum and taking snuff, said that spitting was in a separate category. Dr. HILL, replying to the amendment, said that the clause, in its references to cleanly practices and the like, did give the necessary power to make regulations relating to spitting and smoking. Spitting could be made an offence, punishable by a fine of £5, by local by-law. Should it be made punishable under the clause by a fine of £100 or three months' imprisonment? He doubted whether the best interests of public health were served by so heavy a penalty. Education must play a great part in modifying the conduct of offenders. He offered an assurance that spitting would be included in the regulations, with modified penalties. Smoking should be left where it was, in the code of practice, and something that could be made the subject of local by-law. Dr. SUMMERSKILL welcomed the promise, but said she was not prepared to accept anything less than the inclusion in the Bill of the words she had proposed. Dr. HILL said he would accept the amendment, provided they could examine the words to determine whether they were appropriate. Dr. SUMMERSKILL: No. Dr. HILL: I am doing my best. Dr. SUMMERSKILL: Go a little bit further. Dr. HILL said he had some doubt whether the last part of the amendment was sufficient to do what was intended, and could include the place where utensils were stored. He was anxious that they should be united in their condemnation of spitting, and so he would accept the amendment and look at the words afterwards to see whether they needed changing. The amendment was agreed to.

Advisory Councils

A general discussion took place on a series of amendments proposing the appointment of a Central Food Hygiene Council to advise Ministers on the making of regulations and codes of practice; local clean food committees; a Food Hygiene Advisory Committee, to give general advice on the operation of the Act and other matters referred to them; and a Food Research Advisory Council, to advise on the addition or subtraction of ingredients in food preparation and on processing generally. Mr. HEATHCOAT AMORY thought that the formation of local committees should be left to voluntary action. The suggested central hygiene council and the food hygiene advisory committee did not seem quite right, and he offered to consider the form and functions of both and to bring forward proposals of his own on the next stage of the Bill. He was an advocate of research in general, but thought that to include provision for a research council might cut across useful work already in progress, such as that of the Medical Research Council, with which the Ministry was in close touch.

Before the clause was finally disposed of Dr. HILL said that he was giving consideration to the medical examination of new entrants to the catering trades, which Dr. Stross had reiterated.

The two-day debate ended with a wrangle on the registration of catering establishments. Dr. HILL produced an amendment to Clause 7 (Amendment to S.14 of principal Act) excluding from the registration powers it contained premises used wholly or mainly as catering premises. He said the Government had reached the conclusion that the power of disqualification should be exercised only by the courts after a conviction, and therefore registration of premises was unnecessary. Mr. F. T. WILLEY (Sunderland, North, Lab.) described the proposal as a sell-out to the "dirty food lobby." No one of any repute in the catering industry was afraid of registration. This was the biggest and most cowardly retreat in food hygiene for as long as he could remember. Dr. SUMMERSKILL suggested that the Government had given way at the last moment because a general election was in the offing and they dare not offend all the café proprietors. The amendment was carried by 211 votes to 185.

Reduction in Drug Prices

Mr. A. BLENKINSOP (Newcastle-upon-Tyne, East, Lab.) asked the Minister of Health for a statement on the progress made in securing reductions in the price of proprietary and non-proprietary drugs and medicines. Mr. IAIN MACLEOD said on October 25 that he had told the House in May that the Ministry had not been able to reach agreement on prices with the manufacturers in one group of proprietary preparations. Subsequently agreement for a reduction in prices was reached in the case of two of these preparations, and doctors were asked not to prescribe the two others. Since then, at the request of the Association of British Pharmaceutical Industry, discussions had been proceeding on the general principles by which the prices of proprietaries should be regulated. Cost investigations of the secondary manufacture and compounding of non-proprietary preparations had not so far suggested that the general level of prices in this field was excessive, but the matter was still under discussion. The investigations into the cost of basic drugs were proceeding.

Actions for Compensation

Sir WALDRON SMITHERS (Orpington, Con.) on October 25 asked the Minister of Health, in view of the fact that the total compensation payment made by the Health Service hospital authorities from July 5, 1948, to March 31, 1953, was £328,916, what disciplinary action had been taken against those concerned; and what steps he was taking to minimize neglect or inefficient medical or nursing treatment among

those employed by his department. Mr. IAIN MACLEOD replied that it was for the hospital authorities themselves to determine what, if any, disciplinary action should be taken against members of their staff who were found to have been negligent or inefficient, and to take whatever steps seemed best to them in the circumstances of their own hospitals to minimize the risk of such occurrences.

Breaches of N.H.S. Rules

Miss PAT HORNSBY-SMITH, Parliamentary Secretary, Ministry of Health, stated in answer to Mr. W. W. HAMILTON (Fife, West, Lab.) on October 25 that in England and Wales, between July 5, 1948, and June 30, 1954, four doctors and 25 dentists were excluded from practice in the Health Service, and breaches in the terms of service were found in 573 cases involving doctors and 1,622 involving dentists. Full publicity was given where a practitioner was excluded from practice, but in other cases publication would not in her view be in the public interest.

Partnership Payments

Mr. JOHN RANKIN (Glasgow, Tradeston, Lab.) asked the Secretary of State for Scotland on October 26 if he was aware that certain medical practitioners were taking assistants into partnership on payment of an agreed sum of money in compensation; and what action he would take to put an end to this practice. Commander T. W. GALBRAITH, Under-Secretary, replied that the Secretary of State was not aware of any cases of this kind. The purchase or sale of any part of the goodwill of a general medical practice in the Health Service was an offence, and if Mr. Rankin had evidence of any such transactions he should report them so that prosecution might be considered.

Myxomatosis Immunity

Commander T. W. GALBRAITH, Under-Secretary, Scottish Office, stated, in answer to questions on October 26 about fears of the pollution of rural water supplies from the spread of myxomatosis, that there were no grounds for apprehension. No evidence had been produced since the advisory council reported last March to warrant any change in their view that there was no apparent risk to human health from the disease. Mr. G. R. H. NUGENT, Parliamentary Secretary, Ministry of Agriculture, was asked by Mr. R. F. CROUCH on October 28 for an assurance that there was no danger to humans from eating infected rabbits. He replied that the trade in wild rabbit carcasses had fallen to nothing, but—except for three hares—the evidence was that there had been no infection passing to human beings or any other kind of animal.

Motorists' Eyesight.—The Minister of Transport, replying to a suggestion by Mr. S. AWBERY (Bristol, Central, Lab.) that there should be a code of rules for motorists who needed glasses for driving, said on October 27 that he was reviewing the standards of vision necessary for safe driving following reports from various expert bodies.

Scottish Health Payments.—The total payments by patients in Scotland in 1953–4 for drugs and appliances prescribed by general practitioners was £740,000. The Under-Secretary said on October 26 it was not expected that the current year's figures would be materially different.

Group Practices.—Ninety-five applications for loans from the group practice loans fund had been received, and 30 of these so far approved in principle, the Parliamentary Secretary to the Ministry of Health stated on October 25.

Transistor Hearing-aids.—The Minister of Health stated on October 25 that he was studying the possibilities of providing hearing-aids of the transistor type under the Health Service, but development was in too early a stage for him to reach any conclusions yet.

Hospital Pilfering.—The Minister of Health stated on October 25 that for the year ended March 31, 1953, notified losses of all items of stores and equipment from hospitals due to fraud, theft, or arson amounted to £8,257 in value. Other notified losses, including stocktaking discrepancies, amounted to £188,052, but it was not known how much, if any, of this was due to theft.

Medico-Legal

DEATH FROM DECOMPOSED PARALDEHYDE

[FROM A SPECIAL CORRESPONDENT]

Paraldehyde has been in use for many years as a hypnotic and has been looked upon as fairly safe unless given in gross overdosage. A recent inquest at Doncaster shows that very old samples can become so toxic as to be fatal.

Case Report

A man aged 32 was admitted to the Infectious Diseases Hospital, Doncaster, on July 8 with pulmonary tuberculosis. The disease also involved the left kidney. On August 31 he was given paraldehyde 2 drachms (7 ml.), diluted with 2 drachms of water. He immediately ejected some of the liquid, and complained of burning in his mouth and throat. Thereafter his condition deteriorated and in spite of treatment he died on September 2. The post-mortem examination, carried out by Dr. Gilbert Forbes, of Sheffield, showed that the patient's tongue and roof of the mouth were whitened; the pharynx and oesophagus were covered with a white membrane, most noticeable round the glottis. The mucous membrane covering the epiglottis, larynx, and vocal cords was white and swollen, while underneath there was intense congestion. This condition extended one-third of the way down the trachea. In the lower lobes of both lungs there was non-tuberculous bronchopneumonia. The patient's stomach was not affected, though the upper parts of the oesophagus were. The pathologist concluded that the patient had died from bronchopneumonia due to damage of the upper air passages as a sequel to corrosion by decomposed paraldehyde. There was no evidence that the pulmonary tuberculosis was a cause of death, although it rendered the patient less capable than a healthy person of resisting infection.

Paraldehyde is a polymer of three molecules of acetaldehyde and can be oxidized by atmospheric oxygen to acetic acid, probably through an intermediate stage of peroxide formation. Pharmacists have been aware of the instability of paraldehyde since 1937, when a paper on the subject was read at the British Pharmaceutical Conference by J. S. Toal.[1] But it is doubtful if anyone realized before the present case the extent to which this decomposition could proceed.

Control of Purity

The *British Pharmacopoeia* controls the purity of the drug by means of limit tests for acetaldehyde, acidity, and peroxidized compounds, and stipulates that paraldehyde should be kept in a small, well-filled container, in complete darkness, and stored in a cool place. Toal examined samples from seven manufacturers and found that four did not comply with the pharmacopoeial requirements at the time of purchase, and after two months of storage in the dark only one sample complied with the limit-of-acidity test. He showed that the amount and rate of decomposition were markedly increased when there was an appreciable amount of air in the bottle as compared with well-filled containers. Storage in the dark did not protect against decomposition, but paraldehyde stored in amber glass bottles decomposed less rapidly than that in white glass bottles whether in the dark or light. This may be due to the effect of the different types of glass, as a similar result has been noted with other drugs, such as hydrogen peroxide. Toal recommended the addition of a preservative, and showed that samples containing resorcinol or phenol had kept well for six months. In a later paper[2] he showed that a variety of phenolic compounds would keep paraldehyde well within the *B.P.* limits of purity for at least nine months, while samples of

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[1] *J. Pharm. Pharmacol.*, 1937, **10**, 439.
[2] Ibid., 1939, **12**, 573.
[3] Glaister, J. (1921). *Medical Jurisprudence and Toxicology.* Livingstone, Edinburgh.
[4] *Principles and Practice of Medical Jurisprudence*, 1928, volume 2. Churchill, London.
[5] *British Medical Journal*, 1896, **1**, 19.
[6] *Lancet*, 1905, **2**, 1107.
[7] *Pharm. J.*, 1945, **154**, 271.
[8] Ibid., 1948, **160**, 250.

the same batch deteriorated appreciably during the same time. Since 1948 the *British Pharmacopoeia* has permitted the addition of up to 0.01% of a suitable preservative. Propyl gallate or hydroquinone are generally used.

In the Doncaster case it appears that the sample must have been at least five years old, and about 2 oz. (57 ml.) were stored in a 4-oz. (114-ml.) white glass bottle. Since the cork was badly corroded, the chances of oxidation were great. Subsequent analysis showed that 40% of acetic acid was present. The 2-drachm (7-ml.) dose of paraldehyde therefore contained about 48 minims (3 ml.) of acetic acid.

Glaister[3] states that in glacial form acetic acid acts as a corrosive poison and in dilute form as an irritant. Parts with which the acid comes into contact are softened and rendered of a whitish or pale yellowish colour. Laryngeal complications, because of the volatility of the acid, are commonly found in such cases. The post-mortem appearances are those of a corrosive; the membrane of gullet and stomach will be found to be more or less attacked, and there may be appearances of corrosive action, certainly of inflammatory action, in the upper air passages. He considers the fatal period to be variable but rapid, and quotes a case of 1 fluid drachm (3.5 ml.) of glacial acid having killed a child, while an adult had recovered after having taken 6 fluid ounces (170 ml.).

Taylor[4] refers to a case of suicide due to acetic acid in 1925 and states that he has encountered several accidental deaths due to drinking concentrated acetic acid by mistake. In 1896[5] a 17-year-old girl died thirty hours after taking 1 ounce (28 ml.) of acetic acid and 30 grains (2 g.) of red mercury oxide. In this case inflammation of the larynx and trachea were observed as far as the bifurcation of the bronchi. In 1905[6] a female child, aged 22 months, swallowed a single mouthful of strong acid (not glacial) used for making vinegar and died within 12¼ hours. At necropsy the buccal cavity, pharynx, and oesophagus showed superficial necrosis; they were covered by a whitish membrane which in the oesophagus especially could easily be stripped off, leaving a raw hyperaemic surface. The stomach was not affected beyond a few white puncta present in the cardiac mucosa. Death was from shock due to local injuries rather than any absorption of the poison. In 1945[7] a 9-months-old child died after being given a strong solution of acetic acid in mistake for gripe water. Here the dose could not have been much more than a teaspoonful (3.5 ml.). In 1948[8] a 45-year-old man committed suicide by taking 3 ounces (85 ml.) of glacial acetic acid.

Preventive Measures

Several measures can be taken to prevent a recurrence of this tragedy. The instability of paraldehyde should be made known as widely as possible. The need for drugs to be under the control of a pharmacist, who is the only person with the necessary training and knowledge to ensure their safe storage, is clear. In those hospitals where a pharmacist is in charge of drugs he is legally obliged to inspect the ward drug cupboards every three months, whereas in smaller hospitals no inspection need be made. Since the advent of the Health Service practically every hospital group now has a pharmacist attached to one of the hospitals, and it should be made compulsory for all drugs in all hospitals to be subject to a routine check by pharmacists.

The Services

Colonel (Honorary Brigadier) J. G. Morgan, C.B.E., T.D., J.P., D.L., has been appointed Honorary Colonel of a T.A. Unit, in succession to Colonel J. P. J. Jenkins, O.B.E., T.D., D.L., whose tenure has expired.

Surgeon Commander H. D. Raffan, R.A.N.R., has been awarded the R.N.V.R. decoration.

The *London Gazette* has announced the following awards:

Third Clasp to the Territorial Efficiency Decoration.—Lieutenant-Colonel (Honorary Colonel) G. G. Talbot, O.B.E., T.D., R.A.M.C.

Second Clasp to the Territorial Efficiency Decoration.—Colonel J. L. Hamilton, M.C., T.D., and Major J. H. Richmond, T.D., R.A.M.C.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending October 16 (No. 41) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	13	2	11	0		29	2	3		
Dysentery	507	46	162	3	2	263	45	88	4	4
Encephalitis, acute	1	0		1		5	0	0	1	
Enteric fever:										
Typhoid	8	1	0	0	4	6	2	0	1	2
Paratyphoid	9	1	3 (B)	1		13	6	2 (B)	0	1 (B)
Food-poisoning	270	25		1		274	20		2	
Infective enteritis or diarrhoea under 2 years				15	20				16	42
Measles*	2,801	185	376	68	110	492	13	76	15	32
Meningococcal infection	27	5	8	1	1	33	1	15	0	
Ophthalmia neonatorum	24	1	5	0		28	2	3	0	
Pneumonia†	346	20	139	1	1	245	13	122	1	1
Poliomyelitis, acute:										
Paralytic	50	2	25	3	2	119	8	21	28	12
Non-paralytic	21	0				99	7			
Puerperal fever§	263	37	12	1		225	37	25	0	
Scarlet fever	777	55	140	25	23	786	42	176	32	39
Tuberculosis:										
Respiratory	736	91	131	19				110	15	
Non-respiratory	99	8	25	3				24	3	
Whooping-cough	1,393	80	130	19	13	2,771	190	230	27	26

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	0
Encephalitis, acute		0			0		0			
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	0	0	0	10	1	2	1	3
Influenza	4	0	0	0	0	4	0	0	0	0
Measles		0	0	0	0		1	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	158	39	20	4	2	120	15	16	4	5
Poliomyelitis, acute	0	0			0	7	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	65	11	10	4	2	78	9	14	3	4
Non-respiratory		0	13	0	0		0	4	0	1
Whooping-cough	1	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	199	22	23	7	4	223	24	24	3	19
Deaths (excluding stillbirths)	4,804	731	504	93	145	4,318	566	502	87	141
LIVE BIRTHS	7,709	1168	855	208	387	7,494	1098	818	217	349
STILLBIRTHS	203	25	22			185	27	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment was reported in September, 1954, was 146, compared with 87 in August and 115 (revised figure) in September, 1953.

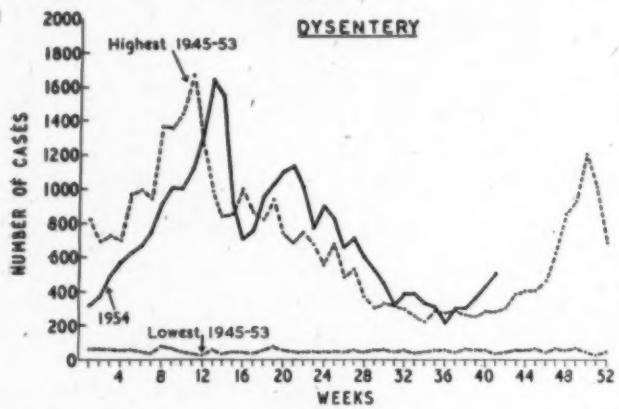
The number of cases of industrial diseases in the United Kingdom reported during September was as follows: lead poisoning 0, other poisoning 3, anthrax 1, epitheliomatous ulceration 17, and chrome ulceration 11; total 32. There were no deaths.—*Ministry of Labour Gazette*, October, 1954.

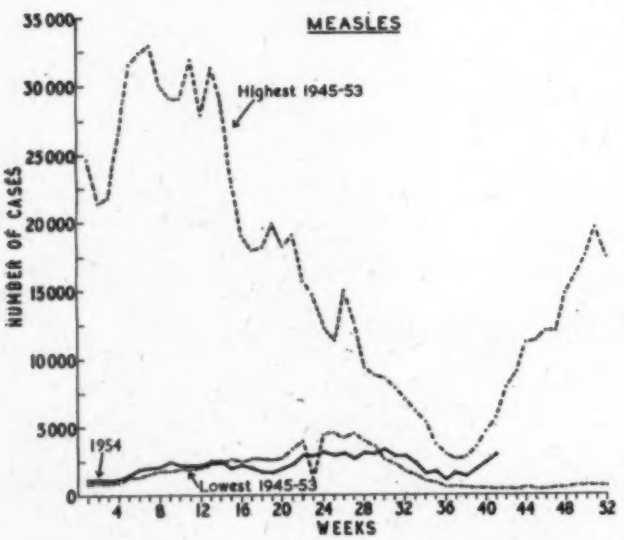
Venereal Diseases

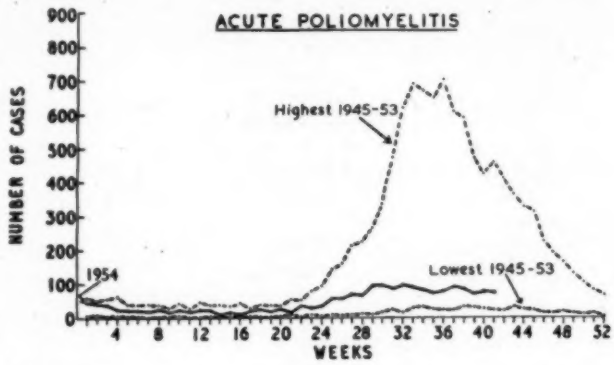
In England and Wales during the quarter ending June 30, 1954, 1,323 new cases of syphilis were reported as attending the clinics. Of these, 180 were classified as primary, secondary, or latent in the first year of infection. 15 cases of congenital syphilis in children aged under 1 year were reported, and 168 cases in persons over that age. New cases of gonorrhoea numbered 4,297, of chancroid 78, and of non-gonococcal urethritis (males only) 3,339.—*Monthly Bulletin of the Ministry of Health*, October, 1954.

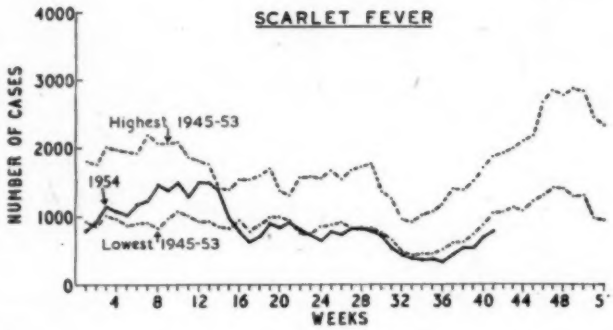
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

A rise occurred in the incidence of most infectious diseases in England and Wales during the week ending October 16. The rises included 443 for measles, from 2,358 to 2,801, 117 for whooping-cough, from 1,276 to 1,393, 96 for scarlet fever, from 681 to 777, and 69 for dysentery, from 438 to 507.

An increase in the number of notifications of measles has been reported for five consecutive weeks, and the incidence is now two and a half times that at the beginning of September. The largest rises during the week were 97 in Durham, from 163 to 260, 92 in Yorkshire West Riding, from 122 to 214, 84 in Somersetshire, from 14 to 98, and 68 in Essex, from 41 to 109. The only rise of any size in the number of notifications of whooping-cough was 47 in Yorkshire West Riding, from 49 to 96. A small rise in the incidence of scarlet fever occurred in most regions; the largest increase was 22 in Lancashire, from 100 to 122. 13 cases of diphtheria were notified during the week, being 2 fewer than in the preceding week.

71 cases of acute poliomyelitis were notified, and these cases were 5 more for paralytic and 6 fewer for non-paralytic cases than in the preceding week. The largest returns were Lancashire 9 (Liverpool C.B. 3), Yorkshire West Riding 7, Gloucestershire 7 (Cheltenham M.B. 6), Durham 5 (South Shields C.B. 2, Washington U.D. 2). In Scotland the number of notifications fell from 31 to 25. 9 cases were notified in both the south-eastern and western regions.

The rise in the number of notifications of dysentery was mainly contributed by Lancashire, where the cases rose from 45 to 125. The largest returns were Lancashire 125 (Oldham C.B. 50, Liverpool C.B. 15, Farnworth M.B. 11), Yorkshire West Riding 71 (Sheffield C.B. 16, Featherstone M.B. 16, Leeds C.B. 12), London 46 (Southwark 12), Glamorganshire 31 (Cardiff C.B. 28), Leicestershire 25 (Leicester C.B. 22), Middlesex 25, Sussex 16 (Cuckfield R.D. 16), Southampton County 16 (Droxford R.D. 14), and Durham 16.

Week Ending October 23

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 749, whooping-cough 1,544, diphtheria 23, measles 3,454, acute pneumonia 400, acute poliomyelitis 62, dysentery 454, paratyphoid fever 6, and typhoid fever 7.

Medical News

Third Volume of "Any Questions?"—A particularly useful feature of the third volume of "Any Questions?" which will be published on Monday is the Cumulative Index to all the answers in the three volumes. Thus those possessing the set can see at a glance where to look up the information they want. The first volume, after a large sale, is now out of print. Volumes 2 and 3 are available from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, price each 7s. 6d. (postage 6d.). Please order on the form inserted loosely in this issue of the *Journal*.

Lord Beveridge on Welfare and Incentive.—Speaking at the golden jubilee conference of the Rotary International at Eastbourne on October 30, Lord Beveridge dispelled some illusions about the Welfare State. He disclaimed either blame or praise for having invented it. The revolutionary change in British policy that had led to the present position dated from the 1906 election of the Liberal and Radical Government, Lloyd George, Herbert Samuel, and Winston Churchill then being the prime movers in this field. In welfare, said Lord Beveridge, some things were for the State, others for the citizen, either individually or in co-operation with other citizens. Two things at least the State must do, else they would not get done: redistribute money incomes by social insurance to eliminate want from sickness, accident, unemployment, or old age; and maintain the value of money. So far as the first was concerned, any form of means test destroyed individual incentive. "Putting up pensions and benefits to subsistence level was laid down in the Beveridge Report not in the spirit of giving from the State to everyone everything he could want, but in the spirit of leaving everyone with incentive to do better than the State." If the value of money were not maintained people lost the incentive to plan their spending and saving. "Whatever the State does," Lord Beveridge said in conclusion, "it must leave room and incentive for the individual to think for himself." This week, on November 5, Lord Beveridge is speaking before a conference of the British Hospital Contributory Schemes Association at Bristol on the more medical aspects of the Welfare State. His address, "The Role of the Individual in the Health Service," will be published subsequently in the *British Medical Journal*.

"Horror Comics."—On November 1 Mr. A. L. Miller, managing director of the Arnold Book Company, the principal publisher of horror comics in England, told a *Daily Mail* reporter that he would sell no more of them. This follows the mounting indignation against these papers which has been voiced by the public, the Churches, the Press, Members of Parliament, and the newspaper trade itself. Last week the Comics Magazine Association of America announced a code of ethics for comic books, which has the support of 26 of the principal publishers of comic books in America. According to the *Daily Telegraph* the total sales of comic books in the United States is in the region of 60 to 70 million copies a month. In Scotland, the Scottish council of the National Federation of Newsagents decided to recommend its members not to handle the comics, and this resolution will be considered by the national council in London.

Leverhulme Research Awards.—Application is invited for fellowships and grants in aid of research. These awards are intended for senior workers of established position and are limited to British-born subjects normally resident in the United Kingdom; in exceptional circumstances the Trustees may waive the condition as to residence. Details and forms of application may be obtained from the Secretary, Miss M. Branney, Leverhulme Research Awards, St. Bridget's House, Bridewell Place, London, E.C.4. The last day for applications is December 31.

Anglo-French Exchange Bursaries.—Applications are now invited for the bursaries which will be awarded in 1955 to young British doctors under the exchange scheme arranged by the French Embassy in London between the Institut National d'Hygiène in Paris and the Ciba Foundation in London. The value of the French grants is 60,000 francs a month, tax free, and they will be awarded for periods of two to four months to medical men who wish to obtain clinical experience or carry out research in France. Preference will normally be given to candidates holding teaching posts. Application forms may be obtained from Dr. G. E. W. Wolstenholme, Ciba Foundation, 41, Portland Place, London, W.1. The closing date for applications is February 5, 1955.

Leukaemia Prizes.—The Robert Roesler de Villiers Foundation is offering 5,000 dollars for a "preventive measure, cure, or control of leukaemia and allied diseases; 1,500 or 1,000 dollars, respectively, for a significant contribution of practical or theoretical value." Details from the Foundation, 1172, Park Avenue, New York, 28.

Grenfell Association.—Attractive Christmas cards and calendars are again offered this year by the Grenfell Association of Great Britain and Ireland, to raise funds for the association's medical work in Labrador and Northern Newfoundland. There is an urgent need to rebuild the hospital established 30 years ago at North West River: the structure is now dangerous and quite inadequate for present needs. Last year over 145,000 cards were sold—a record. Copies of an illustrated leaflet of the cards may be obtained for 1½d. from the association's office at 66, Victoria Street, London, S.W.1.

Welfare Foods.—The token scheme for welfare milk came into operation on October 31. Details of the scheme were given in our issue of June 26 (p. 1505).

Advisory Committee on Medical Research in Scotland.—Sir ANDREW DAVIDSON, formerly Chief Medical Officer of the Department for Health of Scotland, has been appointed chairman in succession to Sir EDWARD APPLETON, F.R.S. (see *Journal*, October 16, p. 936).

News in Brief.—Professor J. B. LEATHES, F.R.S., emeritus professor of physiology, University of Sheffield, celebrated his 90th birthday on November 5. He occupied the Chair at Sheffield from 1915 to 1933. Before that he was professor of pathological chemistry at Toronto.

Sir LIONEL WHITBY, in his presidential address to the International Haemophilia Society in London last month, drew attention to the dangers to haemophiliacs in being too ready to trust in unscientific remedies. He emphasized the need for co-operation and understanding between doctors and these patients.

The offices of the *Canadian Medical Association Journal* have been moved from Montreal to 176, St. George Street, Toronto 5, Ontario.

Stockholm's health is being surveyed by a full examination of a random sample of 3,000 of the city's inhabitants. In addition to clinical examination, the investigations include radiography of the lungs, heart, and alimentary tract, E.C.G. examination, and certain laboratory tests.

Dr. T. J. HONEYMAN, director of the Glasgow Art Gallery, which was visited with enjoyment by many members of the Association at the annual meeting this year, was installed as Lord Rector of Glasgow University on October 29. There were the usual noisy interruptions from students during the ceremony and Dr. Honeyman's address.

Cambridge has now followed Oxford in raising the retiring age of members of the University staff from 65 to 67. In the voting 252 were in favour of the change and 192 against it.

The Battersea Central Mission's clinic for varicose ulcers, which was opened last month by Sir ARTHUR PORRITT, will have special follow-up facilities, including stereoscopic colour photography. The director of the clinic is Dr. STANLEY RIVLIN.

COMING EVENTS

Tobruk Dinner.—Eighth "Tobruk 1941" Officers' Dinner at the Connaught Rooms, London, W.C.1, November 19, at 7 p.m. Tickets, 27s. 6d. (exclusive of drinks), from the Carpathian Brigade Association, 156, Cromwell Road, London, S.W.7.

Nutrition Society.—A symposium will be held at the Middlesex Hospital Medical School, London, on November 20, on "The National Food Survey of Great Britain." Details from Dr. R. J. L. ALLEN, c/o Monkhouse and Glasscock Ltd., Snowsfields, London, S.E.1.

Leeds Medical School Dinner.—On November 26 at 7 p.m. at the Metropole Hotel, Leeds, for past and present male students. Tickets (one guinea) from D. J. GODFREY, The School of Medicine, Leeds, 2.

The Hospitals Symphony Orchestra.—A symphony concert at the Royal College of Surgeons, Lincoln's Inn Fields, November 27, at 7.30 p.m. Further details and tickets (price 10s., 7s. 6d., 5s., and 3s. 6d.) from the College or Miss N. WATTS, St. Bartholomew's Hospital, West Smithfield, London, E.C.1.

Medical Staff Ball, Bethlem Royal and Maudsley Hospitals.—On December 2 at the Connaught Rooms, London, W.C.1. Tickets from Dr. BRIAN ACKNER, The Maudsley Hospital, Denmark Hill, London, S.E.5.

27th General Hospital Reunion.—At the Eccleston Hotel, near Victoria Station, London, on November 27 at 6.30 p.m. Tickets (£1, inclusive of wine) and further details from Dr. L. S. POTTER, B.M.A. House, Tavistock Square, London, W.C.1.

Joint Meeting of British and Canadian Medical Associations.—Owing to cancellations a number of places are still available for the Joint Meeting in Toronto (June 20–24, 1955) for those requiring dollar exchange facilities. Full information from the Secretary of the Association, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 8

INSTITUTE OF CARDIOLOGY.—9.30 a.m., Dr. R. E. Bonham-Carter: Endocardial Fibroelastosis.

●INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. Helen E. Dimsdale: Papilloedema and Papillitis.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor J. Crichton Bramwell: Diagnosis of Rheumatic Valvular Disease.

SOCIETY OF APOTHECARIES OF LONDON.—4.30 p.m., Dr. F. S. Cooksey: Conservative Management of Painful Arthritis; 5.45 p.m.; Mr. H. Lyon-Campbell Wood: Surgery of Painful Arthritis.

Tuesday, November 9

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor Graham M. Wilson: Electrolyte and Metabolic Response to Trauma.

CHELSEA CLINICAL SOCIETY.—At Rembrandt Hotel, Thurloe Place, S.W., 8.30 p.m., discussion: Cancer and Quacks. To be opened by Mr. A. Lawrence Abel and Sir Standford Cade.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Professor R. H. S. Thompson: Enzyme Systems in the Skin.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., clinical meeting.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. C. Scott Russell: Interpretation of Clinical Data.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. G. C. Knight: Diagnosis and Treatment of Spinal Compression.

Wednesday, November 10

HARVEIAN SOCIETY OF LONDON.—8.15 p.m., talk and film demonstration by Dr. Raymond Daley: Cardiac Valve Movement.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Histopathology of Mesenchymal Tumours of the Skin.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. F. R. Kilpatrick: Tuberculosis of the Renal Tract.

LIVERPOOL MEDICAL INSTITUTION.—At St. Paul's Eye Hospital, Liverpool, 3 p.m., afternoon clinical demonstration.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor Frederick Heaf: Advantages and Disadvantages of B.C.G. Vaccination.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. Barbara E. Clayton: Laboratory Investigation in Endocrinology.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH.—5 p.m., Sydney Watson Smith Lecture by Dr. Adam Patrick: Enteric Fevers 1800-1920.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. Macdonald Critchley: Neurology of Old Age (Illustrated).

SOCIETY OF APOTHECARIES OF LONDON.—4.30 p.m., Dr. E. R. Cullinan: Liver Disease and its Treatment; 5.45 p.m., Dr. C. J. C. Britton: Allergic Disorders.

Thursday, November 11

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, W., 8 p.m., Dr. E. N. Snowden: Prevention of Psychoneurosis on a National Scale.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. D. Judah: Enzymes in Injury.

HONYMAN GILLESPIE LECTURE.—At University New Buildings, Edinburgh, 5 p.m., Dr. A. G. Macgregor: Radioactive Iodine in Medicine.

INSTITUTE OF DERMATOLOGY.—5.30, p.m., Dr. R. W. Riddell: Significance of Yeasts in Skin Infection.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. R. Forbes: Recent Developments in Medical Litigation.

OXFORD UNIVERSITY.—At Nuffield Orthopaedic Centre, 8.30 p.m., Professor J. Trueta: Clinical and Experimental Study on Growth of the Long Bones.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Sir William Penney, F.R.S.: Explosions (lantern slides and films)

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Bradshaw Lecture by Dr. F. H. K. Green: Clinical Evaluation of Remedies.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Robert Jones Lecture by Professor R. M. d'Aubigné (Paris): Reconstruction of Joints by Grafts or Prostheses.

ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittington: Factors Affecting Binocular Vision Convergence. Heterophoria.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Medical School, Small's Wynd, Dundee, 5 p.m., Professor B. L. McFarland: Congenital Dislocation of the Hip.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Desmond Curran: psychiatry demonstration.

Friday, November 12

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, St. Bartholomew's Medical College, 2 p.m., scientific papers.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. B. F. Russell: Neurodermatitis.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. N. C. Oswald.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. G. H. Howells: Malignant Disease of the Nose and Nasal Sinuses.

INSTITUTE OF NEUROLOGY.—5 p.m., Dr. Noel Peron (Paris): Familial Ulcerous and Mutilating Acropathies.

OSLER CLUB OF LONDON.—At 11, Chandos Street, W., 7.45 p.m., Opium Evening. Speakers, Dr. J. R. Nicholls, D.Sc.: The History of Opium; Dr. A. E. Clark-Kennedy: Opium in Clinical Medicine; Dr. Douglas Hubble: Opium and Literary Genius; Sir Harry Greenfield, Chairman, Permanent Central Opium Board.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. Guy Blackburn: Pancreatitis.

●ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Dr. Gavin B. Shaw: Management of Hypertension.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Dissertation by Mr. E. W. Horton, B.Sc.: Some Aspects of Cellular Pharmacology.

Saturday, November 13

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—10.30 a.m., Symposium: Rheumatism and Allied Diseases.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Cross.—On October 8, 1954, at St. Giles Hospital, London, S.E., to Margaret, wife of David J. Cross, M.B., Ch.B., of Auckland, New Zealand, a son—Colin James.

Hirst.—On October 14, 1954, at Point-à-Pierre Staff Hospital, Trinidad, British West Indies, to Dr. Anne (formerly Jordan), wife of Major David Hirst, a daughter—Diana Marcia Joan.

DEATHS

Adams.—On October 16, 1954, Evelyn Lancelot Adams, M.B., B.S., of 171, St. James Road, Croydon, Surrey, aged 85.

Banham.—On October 9, 1954, at "Rockley Dene," Worsborough Bridge, near Barnsley, Yorks, Herbert Arthur Luke Banham, L.R.C.P.&S.Ed., L.R.F.P.S., aged 83.

Bastard.—On October 5, 1954, at Fair Park, Bow, Devon, Herbert Rowse Bastard, M.R.C.S., L.R.C.P., aged 70.

Bennett.—On October 10, 1954, at Montreux, Switzerland, Hugh Bennett, M.B., F.R.C.S.Ed., Lieutenant-Colonel, I.M.S., retired, aged 88.

Brodie.—On October 10, 1954, at Invercargill, New Zealand, William Hugh Brodie, M.B., Ch.B., D.P.H., formerly of Penang, Malaya.

Fisher.—On October 15, 1954, at Flat C4, Archers, Archers Road, Southampton, Hants, Victor Laurence Fisher, O.B.E., M.R.C.S., L.R.C.P., aged 57.

Golding.—On October 6, 1954, at 29, Dawson Place, London, W., Marks Golding, L.R.C.P.&S.I. & L.M., D.P.H., aged 66.

Hemingway-Rees.—On October 4, 1954, Mary Isabel Hemingway-Rees, M.B., Ch.B., of 116, Bickenhall Mansions, London, W.

Jackson.—On October 13, 1954, at Hindhead, Surrey, Arthur Ivan Jackson, L.R.C.P.&S.Ed., L.R.F.P.S., D.T.M., formerly of Madras, India, and British Columbia, Canada.

McAlister.—On October 5, 1954, at Rosebank, Dunbar, East Lothian, William Malcolm McAlister, O.B.E., M.B., F.R.C.P.Ed.

Madgwick.—On October 11, 1954, at Johannesburg, South Africa, George Alexander Sheridan Madgwick, M.D., D.T.M.&H.

Merrall.—On October 17, 1954, at 55, Glen Eldon Road, St. Annes-on-Sea, Lancs, Frederic Crompton Merrall, M.B., Ch.B.

Middlemiss.—On October 7, 1954, in the North Staffordshire Royal Infirmary, Stoke-on-Trent, James Ernest Middlemiss, F.R.F.P.S., of Bedale, Sandbach Road, Alsager, Stoke-on-Trent, Staffs, late of Leeds, Yorks.

Murphy.—On October 16, 1954, at his home, 72, Redlands Road, Reading, Berks, Michael Francis Murphy, L.R.C.P.&S.I. & L.M., aged 64.

Park.—On October 15, 1954, at 2, Mansfield Place, Moffat, Dumfriesshire, William Park, M.D., aged 85.

Robertson.—On October 13, 1954, David Robertson, M.B., Ch.B., of Echo Gate, Saltford, near Bristol, Somerset.

Smith.—On October 1, 1954, at 343, Hagley Road, Birmingham, John Hope Robertson Smith, M.B., Ch.B., formerly of Kilchoan, Ardnamurchan, Argyllshire, aged 63.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Effects of the Bad Summer

Q.—*I should be grateful for some information on what effect may be expected from the lack of sunshine during the past summer. Will it tend to increase the incidence of respiratory diseases or lead to any vitamin deficiency?*

A.—It is improbable that the lack of sunshine last summer will have any noticeable effect upon health during the coming months, either in the form of increased incidence of respiratory disease, vitamin deficiency, or otherwise.

The incidence of respiratory disease each winter largely depends first upon whether we have mild or severe—for example, cold or foggy—weather during that winter, and secondly upon whether an influenza or other respiratory epidemic occurs. These two factors, which are not influenced by the weather during the previous summer, would completely swamp any adverse effects that might conceivably result from a less sunny summer than usual.

Thrombophlebitis in Pregnancy

Q.—*If superficial thrombophlebitis is detected during pregnancy or after delivery should anticoagulant treatment be given?*

A.—It is usually best not to give anticoagulants for superficial thrombophlebitis, either during or after pregnancy, unless there is evidence that the process is extending widely and getting out of control. Treatment with such drugs is not safe unless the patient is under constant supervision in hospital. The method is troublesome and expensive and involves some risk of causing bleeding from the placental site, which, if it occurred during pregnancy, would threaten foetal life. Such treatment is therefore not justified for the relatively innocuous if painful condition of superficial thrombosis with or without accompanying cellulitis. Ordinarily in such cases it is best to keep the patient as active as pain will allow (early activity and ambulation in the puerperium, for example), in the hope of limiting the spread of thrombosis.

If at any time there is evidence that the deep veins of the leg are becoming involved then the administration of anticoagulants becomes a matter of urgency. This applies no matter whether the patient is pregnant or recently delivered, the results being very good provided the usual precautions are taken and provided that no anticoagulant other than heparin administered intravenously is employed.

Excessive Salivation after Dental Extraction

Q.—*A man of 54 had all his teeth removed a few months ago as they were unhealthy, and since then has suffered from a continuous and excessive outpouring of bitter saliva from his left parotid gland. Shortly afterwards he was found to be suffering from bronchial carcinoma. What is the probable cause of the excessive salivation, and how should it be treated?*

A.—There are several possible interpretations of these symptoms. Salivation occasionally becomes a troublesome symptom after extensive dental extractions. At times this seems to be comparable to the salivation that occurs in buccal inflammation and in other cases appears to be related to the patient's concentration on his mouth condition and function during the period of dental trouble and treatment. Under these conditions the actual amount of saliva may be increased or the symptoms may really be due to the patient no longer swallowing his saliva either because it is unpleasant to taste or because he thinks it might be harmful.

Secondly, the condition might be due to a mild parotitis following the dental disease or dental treatment. This might well be the case in the present instance if the excessive saliva is really coming from the left parotid gland only, especially as mild parotitis does give rise to a bitter or salty taste in the saliva.

Thirdly, the fact that the patient also has a carcinoma of the bronchus raises the question whether this might be related to the salivation. I have never seen such a case, and in the present instance there is no suggestion of oesophageal involvement.

The presence of a parotitis could be determined by clinical examination and the cytological and bacteriological examination of the left parotid saliva. Small doses of *x* rays might then benefit the symptoms. If a parotitis is not present and the conclusion is reached that the salivation is of a reflex nature, due to a disturbance of local habit, then sedation should be employed in an effort to control symptoms. Any attempt to control the amount of saliva by drugs acting directly on the secretory mechanism of the glands would probably add to the patient's discomfort.

When Does Glandular Fever Cease to be Infectious?

Q.—*After what lapse of time and at what stage of the illness would you say that glandular fever ceases to be infectious?*

A.—In spite of many observations it has not been possible to fix an upper limit for the duration of infectivity. This is probably due to the occurrence of relapses during which infectivity returns after having subsided. There is no doubt that an ordinary simple case ceases to be infectious within a short time. It may be assumed that it is not infectious after the main mass of glands has subsided and the temperature has been normal for one week.

Hormone Therapy for Menorrhagia

Q.—*(a) It has been suggested that menorrhagia may best be controlled by a combination of male and female hormones. Is this correct, and in what type of case is this indicated? (b) If male hormone is given must the husband be told?*

A.—(*a*) Menorrhagia is a symptom and not a disease and is best controlled by treatment directed to its cause rather than by empirical hormone therapy. The more careful the investigation the more often is an organic basis found. Even "functional" menorrhagia is not necessarily caused by an endocrine upset; it may result from a psychological disturbance or from a disorder of the blood or of its circulation in the pelvic organs.

Sex hormone therapy has a limited place except for the temporary control of bleeding, and it should then be used with a clear object in view. Oestrogens can be given to develop an incompletely stimulated endometrium or to raise the blood level of oestrogen above the bleeding threshold. Testosterone may be given to produce temporary atrophy of the endometrium in all manner of circumstances. Preparations containing both oestrogens and androgens are not usually recommended for the control of menorrhagia—not even by the manufacturers of these products who give the indications as climacteric symptoms, absence of libido, dysmenorrhoea, and premenstrual tension. If they are used it is probably because it is hoped that, while the androgen suppresses uterine activity, oestrogen will prevent general virilizing effects—an idea without sound foundation. This objective would in any case be better achieved by giving one of the newer androgen preparations such as androstenediol or androstanolone, which inhibit the endometrium without much risk of inducing masculinity.

(*b*) If androgens in any form are administered, the patient herself should be informed. But, unless she wishes, it does

not appear essential to inform the husband, because if treatment is confined to two or three months, as it should be, the possible side-effects, other than those on the voice, are not permanent.

Splinting a Fractured Femur

Q.—*What is the best way of immobilizing a fractured femur (a) for a short journey to hospital in an ambulance, (b) for evacuation to base under active service conditions?*

A.—(*a*) A fractured femur is most commonly immobilized by a Thomas splint for a short journey. This requires a small range of splint sizes, flannel slings, and clips. Traction, if it can be applied, is useful, but for a short journey bandaging to the splint is quite adequate. However, it may often be impossible to obtain a Thomas splint and the necessary additional equipment. The best splintage under these circumstances is a board which can be bandaged to the side of the body and to the whole length of the leg, thus controlling angulation and rotation. The fracture itself can be rested on a small pillow.

(*b*) Under active service conditions, there is no doubt that the Thomas splint provides the best form of immobilization. "Evacuation to base" usually implies that the primary operation has been carried out. The accepted procedure in the last war for the evacuation of fractured femurs after their initial operation at the forward surgical centre was to apply a Tobruk plaster, which was really a Thomas splint bandaged by plaster-of-Paris.

Pimples Between the Breasts

Q.—*A woman of 30 is greatly troubled by a continual rash of "pimples" on her chest, between the breasts and on their medial aspects. These have not succumbed to simple germicidal ointments, spirit washes, or to some of the proprietary ointments. What treatment is recommended? There is no evidence of hormonal imbalance.*

A.—It seems probable that this is acne vulgaris, though the presence of comedones is not mentioned and it is unusual for acne to be limited to this site. Acne persisting after the age of 20 is often associated with some degree of immaturity, mental if not physical. Degreasing the skin of the affected area twice a day by swabbing with a solution of cetrimide (0.5 to 1%) followed by the application of calamine lotion containing precipitated sulphur (6%) should be tried. Erythema doses of ultra-violet radiation may help, but fractional doses of *x* rays are particularly effective. The general treatment of the patient should not be neglected. A diet low in fat and carbohydrate should be advised and chocolate avoided. Hormone therapy is disappointing.

Normal P–R Interval

Q.—*Authorities vary in the figures given for the normal range of the P–R interval on the electrocardiograph record. What does your expert consider the normal range, and from which lead is it best read?*

A.—The answer to this question can best be given in the words of Sir Thomas Lewis in *The Mechanism and Graphic Registration of the Heart Beat*, 1925, p. 47: "P stands in relation to auricular systole and its up-stroke precedes R by 0.13 to 0.21 of a second, this time interval constituting the P–R interval."

There does not seem to be any reason to depart from this statement, and it is generally considered that the upper limit of the interval is 0.2 second. The measurement should be made in the lead which shows the waves most clearly, particularly the P wave. This is generally standard lead II, or VF, VR, or V_1. The measurement should be made from the beginning of the upstroke of P to the beginning of the ventricular complex: that, of course, may begin with a downstroke, Q, in which case the measurement will be the P–Q interval.

Ringworm from Cattle

Q.—*A virulent type of tinea corporis occurs in my rural practice. Infection presumably occurs through contact with infected cattle. What would be the most effective form of treatment? It would seem that a paint would be most convenient. Would one containing benzoic acid, salicylic acid, and strong iodine be suitable? I shall be most grateful for your opinion.*

A.—Cattle ringworm infection commonly provokes a severe vesicular and pustular reaction, and in hairy parts this takes the form of pustular folliculitis producing the kerion lesion. This reaction tends to throw off the infection and so cure the disease, and is generally to be promoted by the use of heat such as fomentations. Where hairs are involved it is an advantage to remove these manually: they come out with the greatest of ease. The use of fungicides helps and particularly tends to limit spread. Ung. dithranol. *B.P.* is valuable, or the following paint, or the alternation of these measures: Hydrarg. perchlor., 0.5% ; brilliant green, 0.5% ; industrial spirit to 100. A paint alone may cause scabbing and dam back secretion.

Humming in Occluded Ear

Q.—*I have had a complete nerve deafness in my left ear since childhood and am now over 60. When I lie on my right side in bed I hear only sounds that are conducted through the pillows. If I clench my teeth in this position I get a continual hum in my right ear which increases the tighter I clench them. What is the mechanism and what nerve paths are involved?*

A.—As the right ear is occluded so that outside sounds cannot easily be heard, this means that the masking effect of background noise is lost. Therefore, the hearing ear will be much more sensitive to any little sound which may occur within the ear. If, for instance, a person with normal hearing goes into a really soundproof room the result is eerie: often sounds in the ear, probably due to blood flow, will be heard, and I think that it is this mechanism which is causing the sound in this case. Clenching the teeth also causes contraction of the intratympanic muscles, and this would almost certainly produce a temporary change in the noises.

Correction.—The date of the Tenth International Congress of Urology in Athens is April 10–18, 1955, *not* in March as stated in our issue of October 23 (p. 1000).

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